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* *The Mayas of Central America chewed chicle (the basis of today's chewing-gum) more than 1,000 years ago. And they were renowned for their splendid teeth.*

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY APRIL 8 1961

LEUKAEMIA IN CHILDHOOD AND YOUNG ADULT LIFE

TRENDS IN MORTALITY IN RELATION TO AETIOLOGY

BY

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There is good reason to believe that the different clinical and cytological types of leukaemia represent distinct diseases. Thus there are major differences between the age and sex distributions of chronic lymphatic, chronic myeloid, and acute leukaemia (MacMahon and Clark, 1956). Furthermore, ionizing radiations have been shown to cause chronic myeloid and acute leukaemia, but they have not been shown to cause chronic lymphatic leukaemia, and the geographical distribution of the first two types differs from that of the last in that chronic lymphatic leukaemia is relatively rare in the Far East (Wells and Lau, 1960). Finally, recent cytogenetic data have demonstrated the existence of a specific chromosomal abnormality in many cases of chronic myeloid leukaemia, but, so far, not in any other type of leukaemia (Nowell and Hungerford, 1960; Baikie, Court Brown, Buckton, Harnden, Jacobs, and Tough, 1960). Clearly, therefore, the various types of leukaemia should be separated in any study of its aetiology. Until recently this has been possible only in studies based on hospital data. Insufficient details have been published in the national vital statistics for mortality of the various types to be examined separately; moreover, many of the deaths attributed to leukaemia have been certified as due to leukaemia without further specification.

An opportunity to make a more detailed examination of the trends in mortality was provided by the British Registrars-General when they extracted information from the records of all persons certified as dying from leukaemia since 1945 and made it available to the Medical Research Council. This information can be used to re-classify the causes of death in any desired way. The results obtained for adults aged 15 years and over in England and Wales have been published previously (Court Brown and Doll, 1959). The present paper contains similar data for children and for young adults under the age of 30 years. Data for young adults have been included because the mortality from leukaemia is at a minimum between the ages of 20 and 29 years, and this age period provides a natural break between the childhood and adult forms of the disease. Moreover, Lee (1961) has shown that there is a small peak in the mortality from leukaemia at ages 15–19 years, and this is missed if the break is made earlier.

The total leukaemia mortality at these ages in England and Wales has also been examined over a longer period, and some of the data are compared with similar data from other countries.

Results

The mortality from leukaemia in childhood and early adult life varies sharply with age. The extent of the variation is illustrated in Fig. 1, which shows the age-specific death rates for England and Wales for the period 1945–59. A sharp peak in mortality is seen to occur at age 3 years in both sexes, and a smaller peak is shown at ages 15–19 years in males. It seems possible that different factors may be responsible for the production of these peaks, so that it is desirable to examine the mortality in the principal age-groups separately.

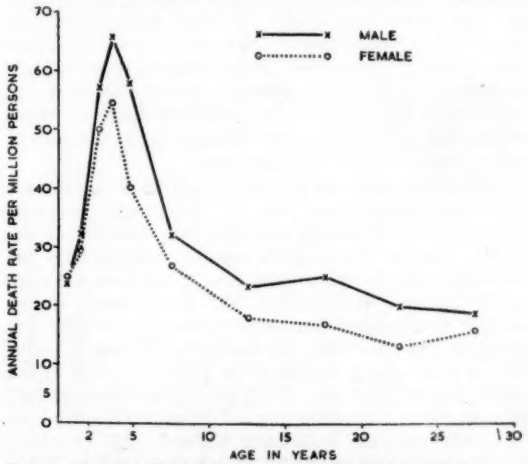

FIG. 1.—Age-specific death rates from leukaemia under the age of 30 years by sex in England and Wales, 1945–59.

Mortality from Different Types of Leukaemia

The deaths recorded during the five-year periods 1945–9, 1950–4, and 1955–9 were classified into nine diagnostic categories: (1) acute lymphatic leukaemia;

(2) chronic lymphatic leukaemia; (3) lymphatic leukaemia of unspecified type; (4) acute myeloid leukaemia; (5) chronic myeloid leukaemia; (6) myeloid leukaemia of unspecified type; (7) other and unspecified acute leukaemias; (8) unspecified chronic leukaemias; and (9) leukaemia without further description. At ages under 30 years, and especially in childhood, chronic leukaemia is extremely rare, and the great majority of the cases described merely as "lymphatic" or "myeloid" leukaemia are likely to have been cases of acute leukaemia. The original nine groups were therefore reduced by combining the data for (*a*) acute and unspecified lymphatic leukaemia and (*b*) acute and unspecified myeloid leukaemia. Similarly it was assumed that unspecified leukaemias were also acute, and they were added to the group of unspecified acute leukaemias.

Finally, the few cases of unspecified chronic leukaemia were allocated to the groups of chronic lymphatic leukaemia and chronic myeloid leukaemia in proportion to the numbers of cases given these specific diagnoses in the corresponding quinquennia and five-year age-groups. By this means mortality rates could be estimated for five types of leukaemia—acute lymphatic, chronic lymphatic, acute myeloid, chronic myeloid, and other and unspecified acute leukaemia. Whether it is useful to separate the acute leukaemias in this way is uncertain. The diagnosis of the various types of acute leukaemia may be extremely difficult, and even after detailed examination by expert haematologists it may be impossible to obtain agreement over the proper classification of a particular case. The description of the type of leukaemia given on a death certificate will not necessarily be based on an expert opinion, and it must be presumed that many of the descriptions are erroneous. Nevertheless, there is evidence of sharp variation in the proportion of the different types of acute leukaemia diagnosed at different ages in childhood and early adult life, and it seems probable that the trends reflect real differences, even though the classification of individual cases may be inaccurate.

The results obtained for the period 1945 to 1959 are shown in Table I and Fig. 2. For acute lymphatic leukaemia the maximum mortality was recorded in the fourth year of life in both sexes. Among boys the mortality rose to more than four times that recorded in the first year of life (7.9 to 33.5 per million); among girls it rose more than three times (9.3 to 29.8 per million). At older ages the mortality fell rapidly, with only a slight check at ages 15 to 19 years. The lowest figure recorded (at ages 25–29 years) was less than half that recorded in the first year. The mortality attributed to acute myeloid leukaemia showed less variation. Among males the mortality varied from 100 to 225% of that recorded in the first year; among females the mortality ranged from 88 to 148%. In both sexes the maximum rate was recorded between ages 2 and 4 years, but there was also a secondary peak, more pronounced in males than females, at ages 15 to 19 years. In view of the inaccuracy of a classification limited to death-certificate data, it is possible that the childhood peak in mortality from acute myeloid leukaemia and the check in the rate of fall of the mortality from acute lymphatic leukaemia in late adolescence are artifacts due to misclassification.

The mortality from chronic leukaemia remained low within the age limits studied, and the variations other than the increase attributed to chronic myeloid leukaemia above the age of 20 years may well be due to misclassification.*

TABLE I.—*Mortality from Leukaemia in England and Wales, 1945–59, Divided by Sex, Age (0 to 29 Years), and Type of Leukaemia*

Sex	Age (Years)	Annual Leukaemia Death Rate per Million					
		Acute Lymphatic	Acute Myeloid	Other and Unspecified Acute	Chronic Lymphatic	Chronic Myeloid	All Types
Male	0	7·9	5·1	11·0	0·2	0·2	24·4
	1	12·5	8·2	11·2	0·2	0·2	32·3
	2	31·5	9·8	14·4	0·9	0·9	57·4
	3	33·5	11·5	17·8	2·1	0·8	65·7
	4	30·9	11·5	14·4	0·4	0·6	57·8
	5–9	15·4	6·0	9·6	0·4	0·4	31·8
	10–14	9·9	6·9	5·6	0·4	0·4	23·3
	15–19	8·8	9·4	6·7	0·2	0·5	25·5
	20–24	6·0	7·6	5·5	0·3	1·0	20·4
	25–29	3·9	8·1	4·4	0·3	2·1	18·8
Female	0	9·3	5·6	10·8	0·0	0·0	25·7
	1	13·3	6·1	9·6	0·4	0·4	29·8
	2	25·6	8·3	14·5	0·5	0·5	49·4
	3	29·8	7·2	16·3	0·7	0·5	54·5
	4	23·2	4·9	11·6	0·4	0·0	40·2
	5–9	12·7	6·2	7·6	0·3	0·2	27·0
	10–14	6·2	6·7	4·4	0·1	0·3	17·7
	15–19	5·0	6·9	4·6	0·0	0·5	16·9
	20–24	3·3	5·4	4·1	0·1	0·9	13·8
	25–29	3·1	6·4	4·4	0·3	1·8	16·0

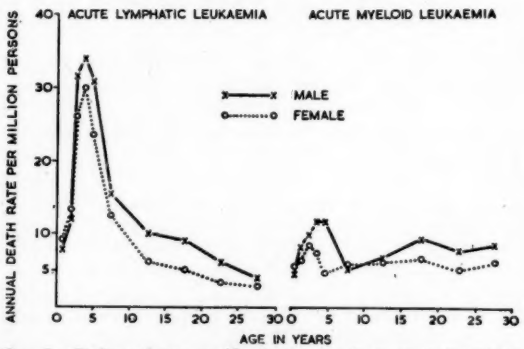

FIG. 2.—Estimated age-specific death-rates from acute lymphatic leukaemia and acute myeloid leukaemia under the age of 30 years by sex in England and Wales, 1945–59.

Trends in Leukaemia Mortality with Time

Leukaemia death-rates for England and Wales by sex and in five-year age-groups have been published for quinquennia from 1911–16 to 1951–5 by McKenzie, Case, and Pearson (1957). Similar figures for the three quinquennia 1945–50 to 1955–9 are shown in Tables II and III. The trends in the mortality with time for the separate five-year age-groups are illustrated in Fig. 3. The rates are shown on a logarithmic scale, so as to facilitate comparison of the relative rates of increase. There is no obvious difference in the trends, save that the rate of increase has been somewhat greater in the youngest age-groups. The average rate of increase over the 50 years examined was approximately 4.5% per annum at ages under 10 years and decreased to less than 4% at ages 20–29 years. In two age-groups (0–4 years and 15–19 years) there was no increase during the last 10 years.

*The estimated rates for the chronic leukaemias at age 15 to 29 years differ slightly from those published previously (Court Brown and Doll, 1959) because the method of allocating the deaths attributed to leukaemia without specification of the clinical type was different. The previous study was concerned with a larger area range, and at older ages the present method would have been inappropriate. At ages 15–29 years, however, the difference in the results obtained by the two methods is trivial and, for the purpose of the present study, can be ignored.

The explanation of these changes is likely to be complex. To a large extent they may be due to improvements in case-finding and to more accurate certification of causes of death, particularly in the early part of the period examined. Stewart (1961) has pointed out that the introduction of sulphonamides and of antibiotics will have allowed a number of cases to become recognizable clinically, whereas previously pneumonia or some other infection might have been fatal during the early and unrecognized stage of the disease. More recently there have been improvements in therapy which may have produced remissions of such length that the relative values of the age-specific mortality rates at the youngest ages have been changed. In our opinion, however, it is difficult to account for the continued increase in mortality at young adult ages by these factors alone, and it seems probable that some of the increase has been due to a true increase in the incidence of the condition.

Trends in the mortality from the various types of leukaemia during the period 1945 to 1959 are shown in Tables II and III. Some increase has occurred in the mortality attributable to both acute lymphatic leukaemia and acute myeloid leukaemia; but this has been largely at the expense of the other and unspecified leukaemias. Changes in the average annual mortality rate for both sexes taken together for ages 0–14 years and for ages 15–29 years are shown in Table IV. In the younger

TABLE II.—*Male Mortality from Leukaemia in England and Wales, 1945–59, Divided by Age (0 to 29 Years), Type of Leukaemia and Period*

Period	Age (Years)	Annual Death Rate per Million Males from: Acute Lymphatic	Acute Myeloid	Other and Unspecified Acute	Chronic Lymphatic	Chronic Myeloid	Total Leukaemia
1945–9	0	8·8	4·1	15·5	0·5	0·0	28·9
	1	13·8	5·8	15·4	0·5	0·0	35·6
	2	26·7	7·8	18·4	2·0	2·0	56·8
	3	31·0	8·5	21·8	3·0	0·0	64·3
	4	27·2	8·2	16·5	1·3	0·0	53·2
	0–4	20·9	6·8	17·4	1·4	0·4	46·9
	5–9	11·5	4·7	9·3	0·3	0·1	25·8
	10–14	9·3	4·1	7·1	0·3	0·1	20·9
	15–19	8·4	7·1	7·7	0·3	0·5	24·0
	20–24	4·0	5·0	6·3	0·4	1·0	16·8
	25–29	3·3	5·0	4·6	0·1	1·3	14·3
1950–4	0	9·9	6·4	9·9	0·0	0·6	26·7
	1	10·9	8·6	10·9	0·0	0·6	31·0
	2	37·4	12·3	13·4	0·6	0·6	64·1
	3	33·2	13·7	20·0	2·1	0·5	69·6
	4	28·6	10·6	16·4	0·0	0·5	56·1
	0–4	24·3	10·4	14·3	0·6	0·6	50·1
	5–9	16·2	5·2	10·1	0·0	0·5	32·0
	10–14	10·1	9·7	4·9	0·4	0·1	25·3
	15–19	9·4	11·7	5·7	0·0	0·3	27·0
	20–24	7·3	8·3	4·3	0·3	1·0	21·2
	25–29	4·6	9·5	4·8	0·1	1·8	20·8
1955–9	0	5·0	5·0	7·3	0·0	0·0	17·3
	1	12·7	10·4	6·9	0·0	0·0	29·9
	2	30·5	9·4	11·1	0·0	0·0	51·0
	3	36·4	11·9	11·3	1·2	1·8	62·6
	4	37·1	15·6	10·2	0·0	1·2	64·0
	0–4	24·0	10·4	9·3	0·6	0·6	44·5
	5–9	17·7	7·8	9·4	0·9	0·7	36·5
	10–14	10·3	6·8	5·0	0·6	0·9	23·5
	15–19	8·5	9·7	6·4	0·4	0·7	25·7
	20–24	6·9	9·7	5·6	0·3	1·1	23·5
	25–29	3·9	8·8	5·3	0·5	3·1	21·7

TABLE III.—*Female Mortality from Leukaemia in England and Wales, 1945–59, Divided by Age (0 to 29 Years), Type of Leukaemia, and Period*

Period	Age (Years)	Annual Death Rate per Million Females from: Acute Lymphatic	Acute Myeloid	Other and Unspecified Acute	Chronic Lymphatic	Chronic Myeloid	Total Leukaemia
1945–9	0	8·7	4·4	9·2	0·0	0·0	22·3
	1	12·3	4·5	10·6	0·0	0·0	27·3
	2	24·0	5·9	18·1	0·3	0·3	48·6
	3	25·5	3·2	14·7	0·3	1·0	44·7
	4	21·2	1·3	11·9	0·7	0·0	35·1
	0–4	17·9	3·9	12·8	0·2	0·2	35·2
	5–9	9·7	3·7	8·7	0·2	0·2	22·4
	10–14	6·7	4·4	5·0	0·2	0·3	16·6
	15–19	5·1	5·0	6·4	0·0	0·3	16·7
	20–24	4·7	3·9	3·4	0·1	0·6	12·7
	25–29	3·0	4·6	3·6	0·2	1·4	12·9
1950–4	0	9·8	7·3	12·8	0·0	0·0	29·9
	1	12·7	7·8	7·2	0·6	0·0	28·4
	2	28·1	6·4	16·4	1·2	0·6	52·6
	3	27·1	10·0	18·8	0·6	0·6	57·0
	4	24·4	7·2	12·7	0·0	0·0	44·3
	0–4	20·6	7·8	13·7	0·5	0·2	42·8
	5–9	13·0	7·0	8·0	0·1	0·1	28·2
	10–14	5·0	6·8	4·1	0·0	0·3	16·2
	15–19	5·2	8·2	3·5	0·0	0·3	17·1
	20–24	4·6	5·2	3·1	0·1	1·5	14·6
	25–29	2·9	7·9	3·3	0·3	1·2	15·6
1955–9	0	9·4	5·3	10·6	0·0	0·0	25·4
	1	15·1	6·1	10·9	0·6	1·2	33·9
	2	24·7	13·0	8·6	0·0	0·6	46·9
	3	37·0	8·2	15·0	1·3	0·0	61·4
	4	23·9	5·7	10·1	0·6	0·0	40·2
	0–4	21·8	7·6	11·0	0·5	0·4	41·3
	5–9	14·8	7·6	6·3	0·5	0·4	29·6
	10–14	6·9	8·4	4·1	0·0	0·4	19·8
	15–19	4·5	7·5	4·0	0·0	0·9	16·9
	20–24	3·2	7·4	3·2	0·1	0·4	14·3
	25–29	3·4	9·6	4·0	0·3	2·7	20·0

TABLE IV.—*Mortality from Various Types of Leukaemia, England and Wales, 1945–9 to 1955–9**

Type of Leukaemia	Death Rate per Million Persons per Year: Ages 0–14 Years 1945–9	1950–4	1955–9	Ages 15–29 Years 1945–9	1950–4	1955–9
Acute lymphatic	12·7	14·9	15·9	4·8	5·7	5·1
,, myeloid ..	4·5	7·8	8·1	5·1	8·5	8·8
Other and unspecified acute ..	10·1	9·2	7·5	5·4	4·1	4·8
Chronic lymphatic	0·5	0·3	0·5	0·2	0·1	0·3
,, myeloid	0·2	0·3	0·6	0·9	1·0	1·5
All types ..	28·0	32·5	32·5	16·3	19·4	20·4

* Mean death rates for three 5-year age-groups in each sex.

younger

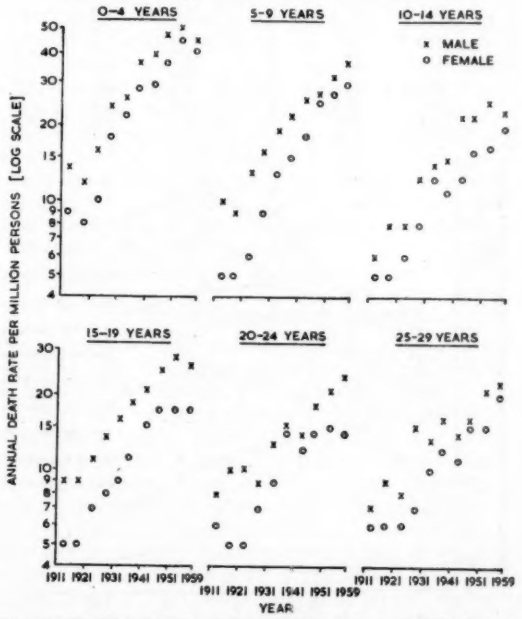

FIG. 3.—Trend in leukaemia mortality with time in England and Wales from 1911–15 to 1955–9 for five-year age-groups from 0–4 years to 25–29 years, by sex.

age-group the changes show that there has been a somewhat greater proportional increase in acute myeloid leukaemia than in acute lymphatic leukaemia, but it would be reasonable to suppose that the increase had affected both types equally and that a greater proportion of the other and unspecified group had been transferred to acute myeloid than to acute lymphatic leukaemia. In the older age-group the position is different. The reduction in the other and unspecified leukaemias is small (5.4 per million to 4.8 per million) and it is smaller than the increase in acute myeloid leukaemia (5.1 per million to 8.8 per million). There is also evidence of an increase in chronic myeloid leukaemia (0.9 per million to 1.5 per million), and it seems likely that at these ages there has been a real increase in the mortality from myeloid leukaemias.

The Childhood Peak

The existence of a peak mortality between 2 and 4 years of age has long been recognized from hospital studies (Cooke, 1942). Mortality data suggest, however, that it has not been present equally at all times nor in all communities. Hewitt (1955) pointed out that the peak became more marked in England and Wales after 1940, and Gilliam and Walter (1958) showed that a similar change occurred among the white population of the U.S.A.; on the other hand no peak was observed among the non-white population.

TABLE V.—*Mortality from Leukaemia in Childhood, England and Wales, 1911–59*

Sex	Period	Annual Death Rate per Million Aged:				
		< 1 yr.	1 yr.	2 yrs.	3 yrs.	4 yrs.
Male	1911–15	9·8	16·5	17·9	14·3	10·6
	1916–20	11·5	14·2	10·7	14·2	11·6
	1921–30	16·4	15·4	20·7	23·4	22·7
	1931–5	19·0	19·2	34·5	28·8	30·5
	1936–9	27·6	36·2	35·3	42·8	39·0
	1940–4	28·1	24·1	40·6	59·5	32·3
	1945–9	28·9	35·6	56·8	64·3	53·2
	1950–4	26·7	31·0	64·0	69·6	56·1
	1955–9	17·3	29·9	51·0	62·6	64·0
Female	1911–15	10·0	12·5	6·4	8·5	5·3
	1916–20	10·0	8·7	9·6	8·0	5·0
	1921–30	12·1	12·0	16·4	15·2	13·5
	1931–5	20·4	24·6	23·6	24·7	16·9
	1936–9	30·5	17·9	32·9	23·0	19·2
	1940–4	27·4	30·7	30·1	36·2	20·7
	1945–9	22·3	27·3	48·6	44·7	35·1
	1950–4	29·9	28·4	52·6	57·0	44·3
	1955–9	25·4	33·9	46·9	61·4	40·2

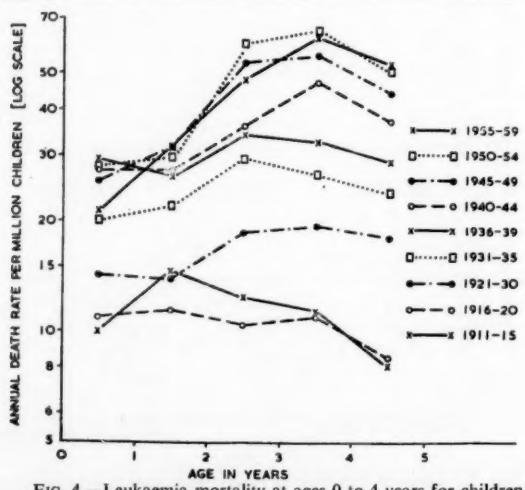

FIG. 4.—Leukaemia mortality at ages 0 to 4 years for children in England and Wales between 1911–15 and 1955–9; mean values for both sexes.

Table V shows the mortality rates for children in England and Wales from 1911 to 1959 for single years of age from 0 to 4 years. Data before 1945 were extracted from the Registrar-General's *Annual Statistical Reviews of England and Wales* and from part III of the *Decennial Supplement for 1921–30* (Registrar-General, 1952). Before 1940 the figures excluded mortality attributed to aleukaemia, which was then classified with Hodgkin's disease; but the number of deaths attributed to Hodgkin's disease in this age-group is so small that the deficiency must be trivial. The shape of the age-distribution curve at different periods is illustrated in Fig. 4; the mortality rates are shown on a logarithmic scale to facilitate comparison of the relative increases at different ages.

From Fig. 4 it is seen that the 2- to 4-year-old peak in childhood mortality was first recorded in 1921–30 and that subsequently there was little change in the pattern of mortality until 1940–4, when the mortality at ages 2 to 4 years again began to rise relative to the mortality at younger ages. As a result, by 1955–9 the mortality at ages 2, 3, and 4 years was approximately double that in the first two years of life.

Among the white population of the U.S.A. the pattern of childhood mortality has been similar (Table VI and Fig. 5). Data are not shown before 1940 because there

TABLE VI.—*Mortality from Leukaemia in Childhood, U.S.A., 1940–58, by Colour*

Population	Sex	Period	Annual Death Rate per Million Aged:				
			< 1 yr.	1 yr.	2 yrs.	3 yrs.	4 yrs.
White	Male	1940–4	47·1	41·7	64·0	57·6	49·9
		1945–9	44·5	45·0	62·6	73·6	63·6
		1950–4	31·7	39·8	65·5	81·6	69·4
		1955–8	23·4	36·9	56·9	78·5	77·6
	Female	1940–4	44·0	36·9	48·3	47·4	41·5
		1945–9	39·0	35·4	55·0	59·5	47·9
		1950–4	33·1	34·7	57·3	71·6	62·6
		1955–8	25·7	35·8	53·2	61·6	68·4
Non-white	Male	1940–4	19·9	15·2	14·6	13·9	11·7
		1945–9	34·2	26·0	21·9	11·0	20·0
		1950–4	35·0	27·6	28·5	27·7	20·7
		1955–8	15·7	28·0	26·1	24·6	27·3
	Female	1940–4	22·3	20·1	13·5	14·0	9·1
		1945–9	19·9	18·2	10·6	17·8	13·5
		1950–4	26·2	27·1	23·1	18·7	20·1
		1955–8	20·9	21·4	18·5	17·5	20·9

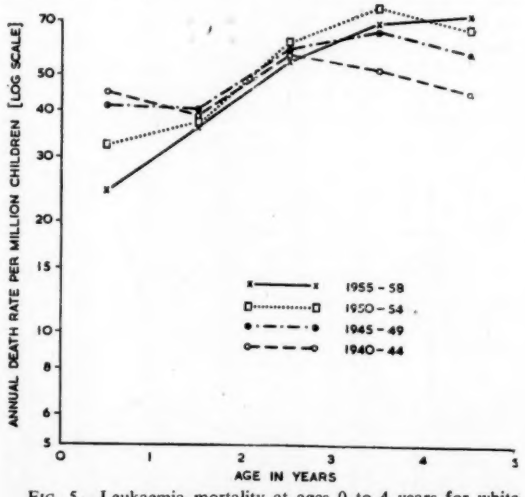

FIG. 5.—Leukaemia mortality at ages 0 to 4 years for white children in the U.S.A. between 1940–4 and 1955–8; mean values for both sexes.

is insufficient information about the size of the population at risk. Since 1940 the death rates have been higher than in Britain but the difference has become less pronounced. In 1940–4 the maximum mortality was recorded at age 2 years; in later periods the peak mortality shifted to age 4 years, and, as in Britain, there was a relative increase in the mortality at ages 2, 3, and 4 years compared with the mortality at younger ages.

The pattern among the non-white population has been strikingly different (Table VI and Fig. 6). At no time has there been any increase in the mean male and female mortality after the second year of life, and in 1940–4 the mortality decreased continuously from the first year onwards. In subsequent periods there has been a relatively greater increase at the older ages, but even in 1955–8 the average mortality at ages 2 to 4 years was very little greater than that recorded at ages 0 and 1 year.

Figures for Japan, provided by the courtesy of Professor Segi, are similar to those for the non-white population of the U.S.A. save that in the most recent period (1955–7) the Japanese mortality has been somewhat higher (Table VII and Fig. 6).

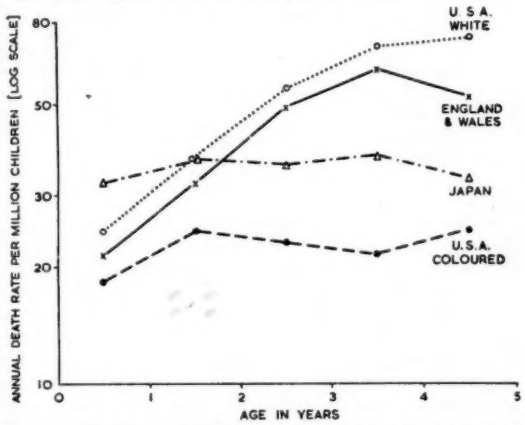

FIG. 6.—Leukaemia mortality at ages 0 to 4 years in England and Wales 1955–9, in the U.S.A. white population and non-white population, 1955–8, and in Japan, 1955–7; mean values for both sexes.

TABLE VII.—*Mortality from Leukaemia in Childhood, Japan, 1940–57*

Sex	Period	Annual Death Rate per Million Aged:				
		<1 yr.	1 yr.	2 yrs.	3 yrs.	4 yrs.
Male	1940–9*	23·6	29·9	18·5	19·1	13·5
	1950–4	26·8	31·2	30·3	27·5	25·6
	1955–7	32·6	43·0	41·5	46·8	36·8
Female	1940–9*	17·7	16·3	15·4	13·7	8·9
	1950–4	23·5	28·1	22·9	17·6	22·7
	1955–7	29·7	29·2	29·1	28·8	29·5

* Data for 1940 and 1947 only.

A comparison of the trends in the relative mortality at ages 2–4 years and 0–1 year is shown in Table VIII. In all four populations there has been a progressive increase in the relative mortality at ages 2–4 years, but there is still no evidence of a peak mortality at these ages in Japan, nor in the non-white population of the U.S.A. In these two populations the distribution of mortality by age in 1950 was similar to that recorded in Britain 30 to 40 years previously.

Burnet (1958) examined the mortality for cohorts of American children born in different years, and concluded that some leukaemogenic factors must have been

TABLE VIII.—*Ratio of the Average Leukaemia Death Rate at Ages 2, 3, and 4 Years to the Average Death Rate at Ages 0 and 1 Year (Male and Female Death Rates Combined); Various Populations, 1911–59*

Period	England and Wales	U.S.A. White Population	U.S.A. Non-white Population	Japan
1911–15	0·86 to 1	—	—	—
1916–20	0·89 ,, 1	—	—	—
1921–30	1·33 ,, 1	—	—	—
1931–5	1·28 ,, 1	—	—	—
1936–9	1·14 ,, 1	—	—	—
1940–4	1·33 ,, 1	1·22 to 1	0·66 to 1	0·77 to 1
1945–9	1·77 ,, 1	1·47 ,, 1	0·64 ,, 1	
1950–4	1·98 ,, 1	1·95 ,, 1	0·80 ,, 1	0·89 ,, 1
1955–9*	2·04 ,, 1	2·11 ,, 1	1·05 ,, 1	1·05 ,, 1

* 1955–8 for the U.S.A., 1955–7 for Japan.

introduced into the U.S.A. about 1942, as the 3-year-old peak in mortality was first evident for children born around that date. As the 3-year-old peak was evident among British children born five years earlier, Doll (1960) concluded that the agent had probably been introduced into Britain before the U.S.A. A more detailed examination of the data, however, throws some doubt on these conclusions.

From Fig. 4 it is evident that there was no sharp change in the age distribution of childhood leukaemia in England and Wales after 1920. Since 1940 the progressive increase in the relative mortality at ages 2–4 years has been shared by other populations, irrespective of the initial age distribution of the disease, and it seems possible that the apparent change in the incidence of the disease may be spurious. Two factors in particular have to be considered. First, improvement in therapy may have resulted in prolongation of life, so that children who are affected at, say, age 2 years may survive temporarily to die a few months later. Secondly, the use of sulphonamides and of antibiotics must have prevented an early death from infection in many cases and so permitted a leukaemic child to survive long enough for the disease to be clinically apparent (Stewart, 1961). There is, however, no obvious similar explanation to account for the change in the pattern of mortality which took place in Britain about 1920, and this may suggest that a new leukaemogenic agent was introduced about this period. The white population of the U.S.A. was presumably exposed at or about the same time, but the negro population of the U.S.A. and the Japanese have either not been exposed or are not susceptible. It is difficult to explain the differences in the age distribution of the disease in these populations by differences in medical care, as there is no consistent difference in the mortality in the first year of life.

The Adolescent Peak

The increase in male mortality at ages 15–19 years illustrated in Fig. 1 has been present in eight out of the nine quinquennia between 1911 and 1955 (McKenzie *et al.*, 1957) and was also present in 1955–9 (Table II). Among girls a similar increase was seen in only four quinquennia. Lee (1961), who first recognized that this peak was not due to random fluctuations, analysed cancer registration data and showed that the irregularity could be entirely accounted for by an increase in a particularly acute type of myeloid leukaemia, in which the duration of symptoms prior to registration was less than two months. That the increase is due principally to a form of acute myeloid leukaemia is also indicated by the mortality data given in Tables II and III and illustrated in Fig. 2.

The occurrence of the peak is not limited to British data, and Lee showed that it was also present in leukaemia mortality figures for the U.S.A. and Canada. Data for 24 countries are given by Segi (1960). In many of these the recorded numbers are too small for useful analysis, and the data shown in Table IX relate only to those populations for which there were more than 30 deaths from leukaemia among males aged 15–19 years during the period 1952–7. In 11 of the 14 populations the male mortality is seen to have been higher at ages 15–19 years than in either of the neighbouring age-groups. It is of interest that the peak is present in Japan and in the non-white population of the U.S.A. despite the absence of a peak in childhood mortality.

Changes in the female mortality are somewhat less marked, but the peak is present in 9 of the 14 populations, and the average increase at ages 15–19 years over the mean for the two neighbouring age-groups is practically the same in each sex (males 126%, females 123%). Some of the increases are substantial (for example, male mortality in Austria and female mortality in Switzerland); but extreme values are likely to occur, due to chance alone, in countries with small populations. There is little correlation between the size of the increase in males and females in individual countries ($r=0.21$), and it is not justifiable to conclude from these figures alone that there is any appreciable geographical variation in the size of the peak.

The latent period for acute leukaemia is of the order of four to eight years when it is induced by irradiation, and, if the duration is the same for other causes, it would appear that the increase at ages 15–19 years was due to an increased stimulus at about the age of 9–13 years.

Sex Ratio

In England and Wales the mortality from leukaemia in the first year of life has been similar in both sexes throughout the period 1931–59. After the second birthday the mortality rate has been consistently higher in boys, and the ratio between the rates for the two sexes has risen to a maximum of about 1.6 to 1 at age 4 years (Table V); at older ages it has fallen and then risen again to approximately the same value at about ages 15–19 years (Tables II and III, and data published by McKenzie *et al.*, 1957). The mortality rates given in Tables VI, VII, and IX show that a similar pattern has occurred in the white and non-white populations of the U.S.A. and in Japan, though in these populations the early peak has been less definite and the age of occurrence irregular. With the exception of the German Federal Republic, the other nine populations, for which age-specific mortality rates are given in Table IX, all show a maximum sex ratio of the order of 1.5–2.0 to 1 between the ages of 15 and 24 years.

Leukaemia in Mongols

The incidence of childhood leukaemia is known to be greater among mongols than among other children (Stewart, Webb, and Hewitt, 1958). In a proportion of cases the fact that mongolism was associated with leukaemia has been recorded on the death certificate, and it has thus been possible to recognize the association of the two conditions in 36 children dying in England and Wales between 1945 and 1959. To these have been added 14 other instances, occurring in the same period, 13 of which were reported through the courtesy of Dr. Stewart and her colleagues. The sex and age distribution of the children at death is shown in Table X.

TABLE X.—*Number of Deaths Attributed to Leukaemia Known to Have Occurred in Mongols, England and Wales,* 1945–59; *Ages* 0–29 *Years, by Sex*

Sex	Period	No. of Deaths Among Mongols Aged (Years):									
		0	1	2	3	4	5–9	10–14	15–19	20–29	All Ages
Male	1945–9	0	2	0	0	0	2	0	0	0	4
	1950–4	0	3	1	1	0	2	0	0	0	7
	1955–9	0	2	4	1	4	1	0	1	0	13
Female	1945–9	0	1	1	1	0	0	0	0	0	3
	1950–4	1	1	2	1	2	0	1	1	0	9
	1955–9	0	2	4	3	2	2	1	0	0	14

As the sex of each child, the age at death, and the date of death are known, it is possible to use the data in Tables II and III to calculate the number of deaths which might have been expected to be attributed to each of the principal types of leukaemia if mongolism was equally associated with all the normal types of childhood leukaemia. On this basis the numbers of deaths attributed to acute and unspecified lymphatic leukaemia, acute and unspecified myeloid leukaemia, other acute and unspecified leukaemia, and chronic leukaemia would have been expected to be 24.7, 11.0, 13.4, and 0.9 respectively. In fact, the numbers of deaths certified as due to these four categories of leukaemia were 22, 14, 14, and 0. In many cases detailed cytological examination would doubtless result in a reclassification of the type of leukaemia. This is, however, presumably also true of leukaemia occurring among children who are not mongols, and unless there is some bias which has resulted in an unusual degree of misclassification among

TABLE IX.—*Mortality from Leukaemia in* 14 *Populations,* 1952–7*; *ages* 0–29 *Years, by Sex*

Sex	Age (Years)	Annual Death Rate per Million Persons in:												
		Canada	United States (White)	United States (Non-white)	Japan	Australia	Austria	Denmark	England and Wales	France	German Federal Republic	Holland	Scotland	Sweden	Switzerland
Male	0–4	54·2	56·5	30·8	35·2	58·0	62·0	64·2	49·5	58·8	50·3	52·3	46·1	60·8	58·9
	5–9	34·8	42·3	20·7	23·5	40·1	28·4	49·9	33·4	41·9	36·7	32·1	33·7	37·9	52·7
	10–14	20·2	26·3	18·0	21·4	24·7	20·0	29·9	23·3	31·6	24·9	24·9	26·7	28·9	28·9
	15–19	34·0	28·0	21·8	23·2	21·9	35·8	32·9	28·3	31·1	25·5	36·5	31·5	27·9	32·2
	20–24	21·4	25·1	21·7	20·2	24·6	15·2	27·8	22·6	31·5	20·1	17·8	25·3	22·8	19·6
	25–29	23·3	24·8	21·6	19·3	18·5	25·0	18·4	20·7	26·0	22·9	23·8	12·2	20·0	20·4
Female	0–4	42·5	52·4	23·4	26·8	52·0	41·7	65·9	43·1	49·5	41·3	45·2	32·0	58·1	51·8
	5–9	27·2	33·4	14·0	16·9	26·6	23·6	26·2	27·7	29·9	27·8	29·0	23·5	46·2	32·9
	10–14	21·3	20·7	12·6	15·0	16·4	17·0	21·8	18·8	23·0	15·3	20·6	18·9	22·3	21·8
	15–19	17·9	19·3	12·8	15·8	18·5	20·9	27·4	17·5	24·3	15·7	19·6	21·3	20·4	32·8
	20–24	15·9	14·5	11·5	13·8	12·0	12·6	14·0	14·8	20·1	14·9	18·3	13·5	13·0	10·1
	25–29	15·7	17·3	12·6	14·3	22·5	15·6	13·5	16·8	21·8	16·2	19·8	13·6	25·8	18·3

* Compiled from data published by Segi (1960).

mongols, it would seem reasonable to conclude that the increased risk of acute leukaemia among mongols applies equally to all the principal childhood types.

Genetic Factors

Several families have been reported in which leukaemia has occurred in 2 or more members of the sibship (Steinberg, 1960; Stewart, 1961). Furthermore, cytogenetic studies suggest that trisomy for autosome 21, the typical cytogenetic lesion in mongolism, is associated with the predisposition of mongols towards acute leukaemia. Such an association is strengthened by recent evidence for a specific chromosome abnormality in many cases of chronic myeloid leukaemia, apparently a deletion, thought also to affect autosome 21.

A more complex situation is that reported by Buckton *et al.* (1960), of a family containing three mongol sibs and one apparently normal sib, the latter dying from leukaemia. Cytogenetic studies showed the mother to have a chromosome count of 45, due to the presence of an abnormal translocated chromosome involving autosome 21 and a large acrocentric chromosome thought to be No. 15. It is now known that such translocations may arise either in the ovaries of the mother conceiving the mongol child, or the mother herself may inherit the translocated chromosome. The possibility has also to be considered that the error may originate in, or be transmitted to, the father; although this appears a less likely event. The presence of the translocation in the parental gonad is considered to increase the risk of non-disjunction of autosome 21 during gametogenesis. Thus the one mongol sib of the above family, who was examined, had a count of 46 including the abnormal translocated chromosome and an autosome pair No. 21. The child was effectively trisomic for 21 and, therefore, phenotypically a mongol. It is not impossible that the "normal" sib, who died from leukaemia, had the same karyotype as the mother, and that the development of the leukaemic state is related to this. On the other hand, the association of leukaemia and mongolism in this sibship could have been due to chance, although this would seem to be unlikely.

Mongolism is an example of one type of genetic factor influencing the development of leukaemia. Other genetic factors could, presumably, be demonstrated by a study of identical twins. If, for example, a gene mutation was important in the genesis of childhood leukaemia, it would be expected that the frequency of identical twins, each dying from leukaemia, would be increased among the children dying from leukaemia. We have attempted to test this by studying the frequency of twins among 5,143 children who died from leukaemia in Britain between 1945 and 1959, and also among 282 children dying from aplastic anaemia within the same period. Since approximately 2 in every 250 children are identical twins it would be expected that if concordance is complete and the incidence of leukaemia falls equally on twins and non-twins there ought to have been approximately 20 pairs of identical twins affected (5143/250). In fact there was no example of twins, both of whom were certified as dying from leukaemia. Only one pair of twins was found; one child was certified as dying from leukaemia at the age of 5 years, while the other was certified as having died from aplastic anaemia two months later. Even if both had died of leukaemia—which may not be the case—and the twins were identical, as it is reported they were, the evidence would suggest that the development of leukaemia in identical twins is an uncommon event.

Summary and Conclusions

An analysis has been made of the mortality rates from leukaemia among children and young adults under the age of 30 years in England and Wales during the period 1911–59. Similar data for other countries have been examined over a shorter period.

Data provided by the Registrar-General of England and Wales enabled the deaths which occurred between 1945 and 1959 to be classified according to the clinical and cytological description of the disease. Estimated mortality rates for acute lymphatic leukaemia showed a maximum at age 3 years in both sexes. At subsequent ages the mortality fell to a minimum at ages 25–29 years, with only a slight check at ages 15–19 years. The mortality from acute myeloid leukaemia varied less sharply, but showed two peaks at ages 2–4 years and 15–19 years. The check in the mortality from acute lymphatic leukaemia in late adolescence and the peak in the childhood mortality from acute myeloid leukaemia may be artifacts due to misclassification. The mortality from both types of chronic leukaemia was low throughout the age range studied, but there was evidence of an increase in the mortality from chronic myeloid leukaemia above the age of 20 years.

Between 1911 and 1959 the mortality increased fairly steadily in each five-year age-group and in each sex. The average rate of increase was approximately 4.5% per annum under the age of 10 years and slightly less than 4% per annum at ages 20–29 years. The age-groups 0–4 years and 15–19 years showed no increase in the last 10 years. Part of the increase is likely to be spurious and due to such factors as better case-finding and improvements in the therapy of infections; but it is difficult to account for the continued increase at young adult ages by these factors alone. Data for the last 15 years suggest that there has been a real increase in chronic myeloid leukaemia and in acute myeloid leukaemia over the age of 15 years.

Before 1920 there was no evidence of a childhood peak in the mortality from leukaemia. A peak mortality was present at ages 2–3 years from 1921 to 1939, and since 1940 the peak has become more pronounced. Mortality rates for the white population of the U.S.A. since 1940 have been similar, but at a higher level. Peaks in the childhood mortality have not been observed in the non-white population of the U.S.A. or in Japan.

In England and Wales the male mortality from leukaemia showed a small peak at ages 15–19 years in 9 out of 10 quinquennia between 1911 and 1959; among girls a similar increase was seen less often. An increase in mortality in this age-group has been observed in one or other sex in 13 other populations; in some countries the increase has been more marked in women than in men, and, on average, the proportionate increase over the two neighbouring age-groups has been practically the same in both sexes.

The mortality rate from leukaemia in the first year of life is similar in both sexes. At subsequent ages the male mortality has been higher. In England and Wales the ratio of male to female mortality has been highest at age 4 years and at about ages 15–19 years. In nearly all the other countries studied there is evidence of a high ratio between the ages of 15 and 24 years.

Fifty instances of leukaemia in association with mongolism are known to have occurred in England and Wales between 1945 and 1959. The proportion of deaths attributed to the various types of leukaemia are closely similar to those estimated from the national mortality rates, and it is concluded that the increased risk of acute leukaemia in mongolism affects all the types of the disease commonly observed in childhood.

Examination of the death entries relating to 5,425 children who had died of leukaemia or aplastic anaemia revealed only one example of the occurrence of one or other disease in both members of a pair of identical twins.

We are grateful to the Registrar-General of England and Wales for the extraction of the data; to Professor M. Segi for details of the leukaemia mortality in childhood in Japan; to Dr. Alice Stewart for details of some of the cases of associated mongolism and leukaemia; to Dr. R. A. M. Case for information about the mortality rates for leukaemia in childhood in England and Wales between 1911 and 1930; and to Dr. A. G. Gilliam for information about population estimates in the U.S.A. We are grateful also to Dr. Jean Kennedy, Mrs. V. Peetz, and Mrs. J. Pixner for assistance in the analysis.

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"The late Dr. Robert Scot Skirving, a self-styled 'remembrancer' of Australian medicine, spoke of Joseph Bancroft [1836–94] with reverence and admiration. 'There seemed to be nothing in the friendly, untidy town that was Brisbane,' he said, 'that Bancroft was not connected with in some way or other. He knew a lot, and always made it his job to be helpful. He was consulted by everyone in the place, from the Government down. He was just the man for a new country.' The final observation of this wise and critical physician is especially revealing of the characters that brought esteem to Bancroft in his day, and raised the Bancroft tradition. He was just the man for a new country—this is the sum of all his qualities. It includes his deep knowledge and searching mind, his resourcefulness, his self-reliance, and his untiring industry; it includes the extreme utilitarianism that was his hall-mark, and his widely diversified interests; and it surely includes his dedication to his profession and his scientific aims, his full acceptance of community responsibilities and his leadership in all fields of interest. These are the foundations of the Bancroft tradition—the tradition of a great colonial doctor." (Professor Edward Ford, Bancroft Memorial Lecture, *Med. J. Aust.*, February 4, 1961.)

ACUTE MYELOID LEUKAEMIA IN ADOLESCENTS

BY

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The death-rate from leukaemia is high in young children, and then falls to a minimum in early adult life. In the course of studies on morbidity and mortality in adolescents (Lee, 1961) it was noticed that in males the decline in the leukaemia death-rate during adolescence was interrupted by a transient rise (Fig. 1). This excess mortality is not a new phenomenon, but goes back at least to 1911–15. A study of this phenomenon is now reported.

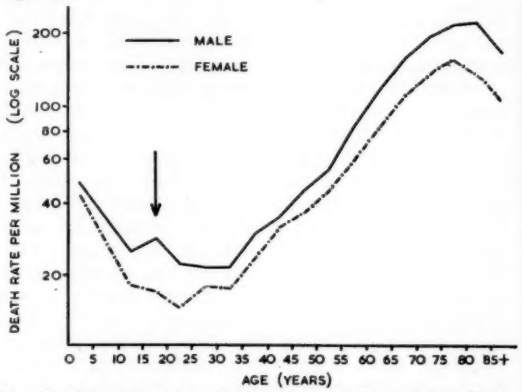

FIG. 1.—Death-rates from leukaemia in males and females by age. England and Wales, 1950–58 (General Register Office, 1957; 1958).

Method

The General Register Office for England and Wales, the General Registry Office for Scotland, the United States National Office of Vital Statistics, and the Canadian Dominion Bureau of Statistics were asked to provide the number of deaths certified to leukaemia by single years of age, over the range 0–29, for as many calendar years as possible. Figures for 1945–57 in England and Wales, for 1950–58 in Scotland, 1950–57 in the United States, and 1949–58 in Canada, were obtained, together with the corresponding population estimates, through the courtesy of these offices.

Leukaemia is not a common disease, and to obtain adequate numbers the data for the whole of the periods available have been combined. In the analysis of mortality, two-year age-groups were found to be a suitable compromise between single years of age, which resulted in too great variations due to small numbers, and conventional five-year age-groups, with their possible obscuring of changes limited to short periods of life.

Further data were provided for 1949–57 through the courtesy of the National Cancer Registration Scheme for England and Wales. A substantial and growing proportion of the cases of malignant disease are reported to this registration scheme, but during these years the number of cases of leukaemia reported in persons aged 15–19 was only about 40% of the deaths certified to leukaemia in England and Wales. Thus division by five-year age groups was the smallest that could usefully be made of these data. Much more information was available about these cases than can be derived from the

analysis of death certificates—for example, on the duration of the illness.

Results

Analyses of the mortality data are shown for England and Wales, for Scotland, for the United States, and for Canada in Fig 2. In each of these four countries the decline of the death-rate with age stops at about 13 in males, and then rises to a new peak at about 17. A

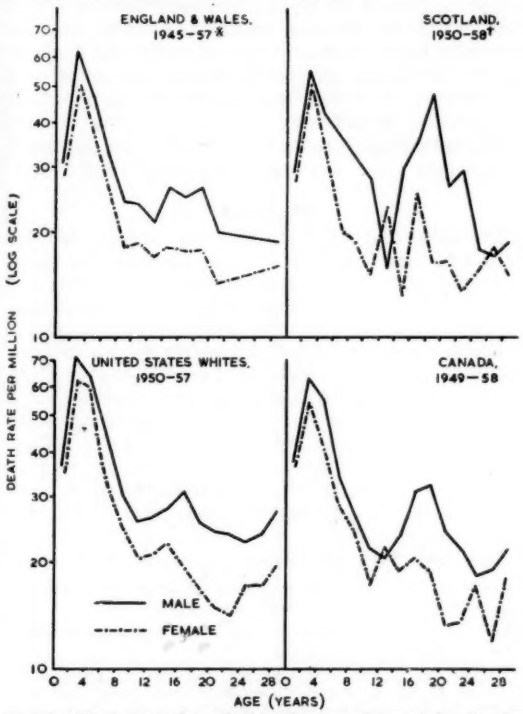

FIG. 2.—Death-rates from leukaemia in males and females by age. (*5-year age-groups 20–24 and 25–29, due to lack of official population estimates. †Based on small numbers).

further decline then occurs, and continues until the late twenties. In females there is evidence of a similar trend, but it is less marked. In the United States and Canada the rise in females appears to occur earlier than in males.

The data from the National Cancer Registration Scheme show a small increase in all leukaemia in males aged 15–19, compared with neighbouring age-groups (Table I). This rise is restricted to cases described by the physician as "acute." Further, these extra cases in male adolescents are concentrated among the acute leukaemia cases with histories of less than two months between the reported onset of symptoms and admission

TABLE I.—*Number of Cases of Leukaemia Notified to the National Cancer Registration Scheme*, 1949–57

Age:	<5	5–	10–	15–	20–	25–	30–	35–	40–	45–49
Male										
Acute ..	178	116	78	87	69	49	44	63	75	80
Other and unspecified	66	54	44	47	56	96	100	121	184	246
Total ..	244	170	122	134	125	145	144	184	259	326
Female										
Acute ..	132	83	59	43	34	39	41	44	39	49
Other and unspecified	56	48	26	38	42	63	70	112	146	213
Total ..	188	131	85	81	76	102	111	156	185	262

TABLE II.—*Number of Cases of Leukaemia Specified as Acute with Histories of Less than Two Months and Number with Longer or Unspecified Histories. National Cancer Registration Scheme*, 1949–57

Age:	<5	5–	10–	15–	20–	25–	30–	35–	40–	45–49
Male										
Acute with history of under 2 months ..	90	51	37	52	29	18	**16**	25	33	27
Acute with history of other and unspecified duration ..	88	65	41	35	40	31	28	38	42	53
Female										
Acute with history of under 2 months ..	73	41	23	19	13	15	13	12	14	15
Acute with history of other and unspecified duration ..	59	42	36	24	21	24	28	32	25	34

TABLE III.—*Number of Cases of Leukaemia Specified as Acute, by Length of History and Cell Type. National Cancer Registration Scheme*, 1949–57

Age:	<5	5–	10–	15–	20–	25–	30–	35–	40–	45–49
Male										
History of under 2 months:										
Myeloid ..	17	9	10	27	14	2	12	12	15	16
Lymphatic	32	23	18	10	8	9	2	6	8	6
Other and unspecified	41	19	9	15	7	7	2	7	10	5
History of other or unspecified duration:										
Myeloid ..	17	11	11	13	16	15	14	21	24	28
Lymphatic	29	23	19	11	12	4	6	7	4	8
Other and unspecified	42	31	11	11	12	12	8	10	14	17
Female										
History of under 2 months:										
Myeloid ..	10	11	5	10	5	4	9	7	8	5
Lymphatic	32	14	6	6	3	2	2	3	0	2
Other and unspecified	31	16	12	3	5	9	2	2	6	8
History of other or unspecified duration:										
Myeloid ..	11	9	10	8	10	14	16	20	11	21
Lymphatic	22	18	11	4	6	6	6	4	5	5
Other and unspecified	26	15	15	12	5	4	6	8	9	8

to hospital (Table II).* Analysis of these cases of acute leukaemia with particularly short histories by cell type shows that the excess at age 15–19 is not found in the lymphatic type, but only in those of myeloid type (Table III, Fig. 3). Moreover, those of myeloid type with a longer history do not show the effect either. The age distribution of these cases of acute myeloid leukaemia with short histories is quite different from that of the rest of leukaemia.†

*The length of survival after diagnosis of the cases notified to the National Cancer Registration Scheme was also recorded, but the method of tabulation was changed in the middle of the period of observation. There are not enough cases in either of the series thus produced for an analysis to be made of survival by five-year age-groups. However, an analysis by ten-year age-groups suggests that short histories before admission do go with short survival.

†Comparing acute myeloid leukaemia with a short history with the rest of leukaemia, using the male data of Tables I–III, $\chi^2 = 48.6$, 9 d.f. $P<0.001$. The contribution to the total χ^2 of the age-group 15–19 alone is 33.3. Only two cases of acute myeloid leukaemia with a short history were notified in males aged 25–29; as the result this age-group makes a contribution of 7.4 to the total χ^2. The small number of cases in this age-group is an isolated finding which requires confirmation before its interpretation can be attempted.

Because the National Cancer Registration Scheme did not include all cases, and the cases included might have been unrepresentative, it was necessary to check the indication that it is myeloid and not lymphatic leukaemia that is responsible for the rise in adolescents. The published national mortality data for leukaemia are divided by cell type but are not divided into the acute and chronic forms of the disease. However, for ages from 15 a special analysis including this division has been made by Court Brown and Doll (1959). In addition, I have assumed that from 0–14 the published deaths were all due to acute leukaemia, chronic leukaemia in this age-range being uncommon (cf. MacMahon and Clark, 1956; Witts, 1956). The death-rates from acute lymphatic leukaemia show a fairly steady decline from childhood to at least the age of 30 (Fig. 4). In contrast, the rates for acute myeloid leukaemia show a rise in males aged 15–19 (Fig. 4).

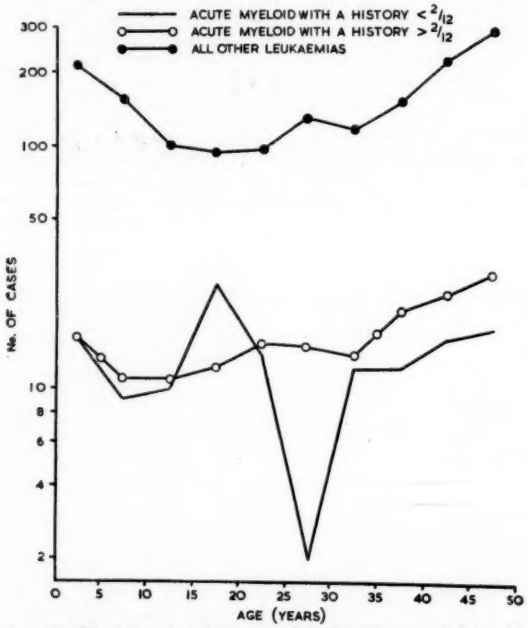

FIG. 3.—Number of male cases of leukaemia reported to the National Cancer Registration Scheme, 1950–57, by age.

Thus in England and Wales, Scotland, the United States, and Canada, males in their teens have an increased mortality from leukaemia compared with neighbouring age-groups. This effect is wholly or almost wholly accounted for by an increased incidence of a form of acute myeloid leukaemia which runs an especially short course before admission to hospital. Chronic leukaemia and acute myeloid leukaemia with a history of more than two months do not appear to contribute to this increase.

The same phenomenon is found in females but is less conspicuous, and it may occur at an earlier age.‡

Discussion

The data from England and Wales suggest that the death-rate from leukaemia in males aged 15–19 is about 6 per million per annum greater than would be expected if the trend of the rates with age was not interrupted in this period (Fig. 2). The male population of this country in this age-group is 1.4 million, so that the whole effect described in this paper is due to about 10 cases occurring annually. This figure gives a measure of the difficulty of studying the problem. However, the smallness of the numbers is due to the rarity of leukaemia of any sort rather than to the smallness of the increase in adolescents. Inspection of Fig. 2 suggests that the death-rate in males is increased by about 25% during this period.

Relatively high death-rates at ages 15–19 from leukaemia in males have been present in England and Wales since at least the early 1910's. The peak has not moved along the age scale, and

‡The excess myeloid leukaemia in adolescents is most obvious in males, and it would be expected that the sex ratio of all leukaemia at this age would be altered by these cases. This may happen, but the effect is lost in a large rise in the ratio of male to female cases of leukaemia which occurs at this age, and which is not restricted to the myeloid cell type. This has a wider age-range than these special cases of acute myeloid leukaemia with a short history, and seems to be part of a quite different phenomenon. A study of these changes is in progress.

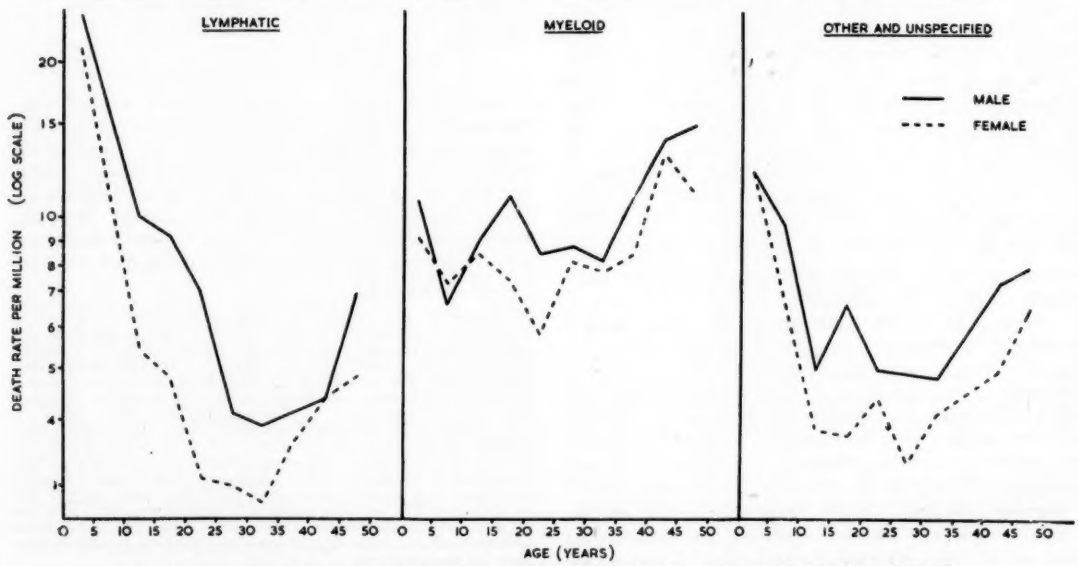

FIG. 4.—Death-rates from acute leukaemia in males and females by age, England and Wales, 1950–57.

thus a "cohort effect" is not present. Since that period, death-rates from leukaemia have risen at all ages, but they have risen at least as much at 10–14 and 20–24 as at 15–19. The peak in adolescents is therefore unlikely to be due to the same causes that have produced the rise in the death-rate from leukaemia at all ages in recent decades. There is no evidence on which to base any discussion of the relationship of these cases of leukaemia to radiation.

The high leukaemia rates in male adolescents are matched by corresponding increases in admissions to hospital for acute infections of the lower respiratory tract (Fig. 5). In females the rise in the number of hospital admissions for these conditions is similar, but, as already pointed out, in England and Wales at least

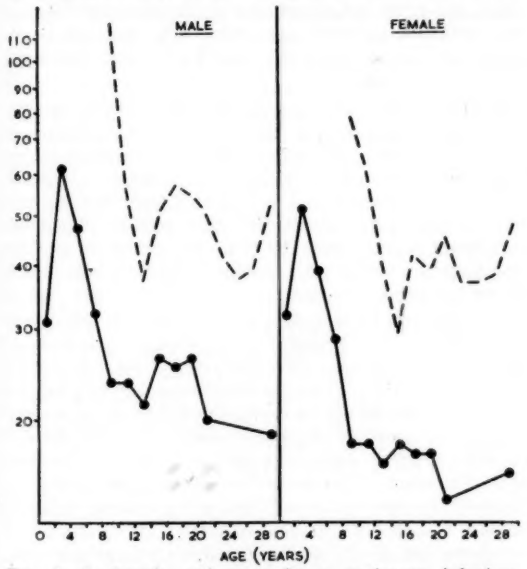

FIG. 5.—Leukaemia and acute lower respiratory infections. ----, Hospital admissions for bronchitis and pneumonia: National Hospital In-patient Inquiry, England and Wales, 1953–56. ●——●, Leukaemia death rates, England and Wales, 1945–57.

the change in the female leukaemia rate is less marked. These are interesting findings, because in children under the age of 10, Stewart (1961) has put forward evidence that pneumonia may induce leukaemia after a short latent period. There is very little other evidence on the possible causation of a special form of leukaemia in adolescents; but it is perhaps worth mentioning that myeloid leukaemia is a disease of bone-marrow, and that the incidence of malignant disease of bone is much higher in adolescents than in children or young adults (Fig. 6). Adolescence is a period of rapid bone-growth (cf. Tanner, 1955; Furth, 1959), and a period when lymphoid tissue regresses—and there is no increase in lymphatic leukaemia. The known causes of leukaemia are few in number, and only a small proportion of cases can be associated with them (*B.M.J.*, 1960; Gunz, 1961). There is a factor which affects adolescents specifically, and which produces a substantial increase in the death-rate from a particular form of leukaemia. There is no reason to associate this with any of the known causes of leukaemia.

The identification of a syndrome by the study of the characteristics of cases in relation to the population from which they come is a typical and successful use of modern epidemiology (Morris, 1957). Further, with a rare disease such as leukaemia the accumulation of data by such means as cancer registries is essential. Both these techniques have been exploited in this study, and it is difficult to see how these special cases of myeloid leukaemia could have been found without them. But studies such as these are dependent on mortality and morbidity data being routinely compiled and made available in sufficient detail for the necessary analyses to be made.

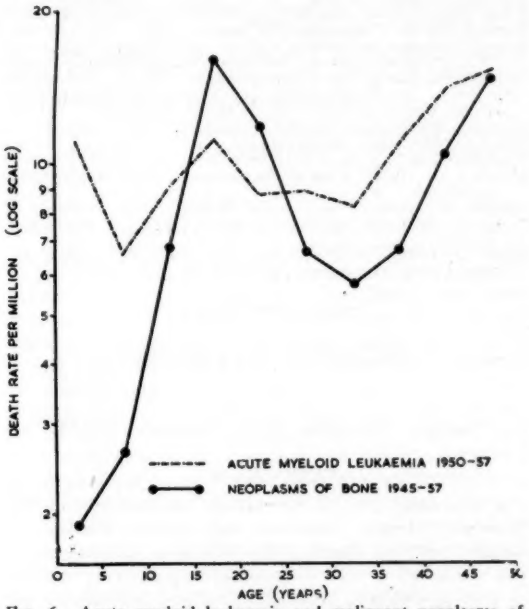

FIG. 6.—Acute myeloid leukaemia and malignant neoplasms of bone in males by age, England and Wales.

Summary

The death-rate from leukaemia in males in their late teens is higher than expected in England and Wales, in Scotland, in the United States, and in Canada. In England and Wales in the years 1945–57 the male death-rate per million per annum was as follows:

Death Rate from Leukaemia in Males (Ages in Years)

6–	8–	10–	12–	14–	16–	18–	20–24	25–29	30–34	35–39	40–44
32·0	24·2	24·0	21·5	26·1	25·0	26·4	20·1	18·5	21·7	25·9	31·3

The effect in females was less marked.

In the National Cancer Registration Scheme for England and Wales the number of male cases diagnosed as acute myeloid leukaemia which had histories before admission of less than two months rose from 10 at ages 10–14 to 27 at ages 15–19 and then fell to 14 at ages 20–24. No similar excess was found in cases with longer histories or other cell types.

The death-rate from leukaemia thus is raised in late adolescence, particularly in males; and this seems to be due to an increased incidence of a form of acute myeloid leukaemia with a short history before admission to hospital.

I am grateful to the General Register Office of England and Wales, to the General Registry Office of Scotland, to the Chief of the United States National Office of Vital Statistics, and to the Canadian Dominion Statistician, for the tabulations of mortality and the population tables that

went with them. The Medical Records Officers of the London Hospital and St. Bartholomew's Hospital kindly supplied data about their cases of leukaemia. The late Dr. A. Mackenzie, of the General Register Office, suggested the analysis of the cases by length of history and was most helpful in other ways. Dr. Richard Doll kindly made analyses of mortality data available. Professor J. N. Morris and my colleagues in the Social Medicine Research Unit and the London Hospital gave me much help.

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ACCIDENT NEUROSIS*

BY

HENRY MILLER, M.D., F.R.C.P., D.P.M.

LECTURE II

The preceding lecture comprised an account of the incidence, clinical features, and natural history of accident neurosis, based on the records of personal cases. The syndrome is seen to present a unique combination of clinical features, amongst the most remarkable of which are an inverse relation to the severity of the provoking injury; an unexpectedly inconstant correlation with neurotic predisposition; scanty objective signs of emotional disturbance; a differential social incidence; and an absolute failure to respond to therapy until the compensation issue was settled, after which nearly all the cases described recovered completely without treatment. These are observed facts, but a consideration of the nature of the syndrome raises more difficult matters of interpretation and speculation.

In subjecting this material to critical scrutiny the first question may well be, how far is there such a thing as accident neurosis? Is this anything more than a convenient label of the kind often employed to spare the investigator further thought about a difficult clinical problem—in this instance the behaviour of a heterogeneous minority of people injured or otherwise involved in accidents? It was with considerable scepticism on this score that I began the present study several years ago. The reader must judge how far the evidence already presented supports my conclusion that, after patients suffering from other definable psychiatric disorders have been excluded, the behaviour of a minority of those involved in accidents is sufficiently characteristic and predictable to justify the acceptance of accident neurosis as a clinical entity. The condition probably affects between a quarter and a third of the victims of accidents which fulfil two conditions. First, the accident must be due to someone else's fault, at any rate in the patient's estimation. Secondly, it must have occurred in circumstances where the payment of financial compensation is potentially involved.

Cursory mention is made in the psychiatric literature of cases in which the syndrome is said to have followed accidents which satisfied the first but not the second of these criteria. Depressive illnesses of endogenous pattern may certainly follow accidents innocent of any financial implications, and very occasionally frank neuroses of anxiety type have been similarly encountered after frightening accidents to predisposed patients, limited in duration and responsive to therapy. It is possible that the florid syndrome of accident neurosis outlined above, with its disproportionate disability and absolute resistiveness to treatment, occasionally occurs after accidents occurring under emotionally loaded circumstances in which no question of financial compensation is concerned, but such cases have not been personally encountered.

Whatever the cause of accident neurosis, it is not the result of physical injury. It may develop without any injury at all, it is comparatively uncommon where injury has been severe, and it is characteristically a complication of minor or trivial injury. Indeed, the inverse relationship to the severity of injury clearly evident in the material described above is crucial to its understanding, and makes nonsense of some "explanations" of the condition.

It is difficult to believe, for example, that any form of constitutional difference between those severely and those trivially injured can account for the apparently "protective" effect of severe trauma against the development of neurosis in these patients, most of whose injuries are sustained in similar industrial circumstances, equally subject to whatever emotional loading is implicit in the employee–employer relationship in such situations. Another interpretation is that the genuinely injured patient, reasonably confident of justice in the matter of compensation, does not need a neurosis, while the grazed or frightened workman develops neurotic symptoms which inflate his trivial or non-existent physical disability to dimensions justifying financial compensation.

But why do only a third of those involved in minor accidents succumb to accident neurosis? The only factual evidence is that such a development is favoured by a low social and occupational status, and that its relationship to a history of psychoneurotic predisposition is surprisingly inconstant—a feature which distinguishes it from almost every other disabling neurosis beginning during adult life, and one which must be regarded as highly significant in any consideration of the nature of the syndrome.

The occurrence of accident neurosis in predisposed subjects is anything but surprising, and the role of predisposition in the persistence of disability after settlement has been demonstrated in the figures already given: of the five patients in whom the condition persisted, four were grossly predisposed to neurosis. However, many patients with accident neurosis have carried on their work for many years before the accident without any trace of psychiatric disability and with little loss of time. Indeed, this feature is often quoted in court to support the genuineness of the patient's complaints. Why do a minority of such patients develop this disabling syndrome? An orthodox psychiatric explanation is that the trivial injury, or the concatenation of circumstances surrounding it, implies devastating

*From the Milroy Lectures for 1961, delivered before the Royal College of Physicians of London on February 7 and 9. Lecture I appeared in last week's issue.

stress for the individual concerned, because of some hidden constitutional vulnerability. Like many such hypotheses, this view is plausible but unsupported by positive evidence. An alternative interpretation is that accident neurosis represents a unique psychiatric disorder or a very special pattern of behaviour.

The differential class incidence of accident neurosis suggests that predisposition to its development might perhaps be conceived in social rather than in formal psychiatric terms. Again, however, this social gradient is open to several interpretations. Some observers endow the economic insecurity of patients in the lower-income groups with a central role in the aetiology of accident neurosis, which they consider in essence a result of anxiety concerning who will accept liability for the care of the patient's dependants during his disablement—a view which also gains some support from the sex incidence of the condition. However, there is a good deal of evidence against it.

Even in social classes IV and V, accident neurosis is not seen after similar injuries sustained where the question of compensation does not arise, though its occurrence under such circumstances might reasonably be expected if the causal anxiety were primary and without motivation. Secondly, it is hardly compatible with the categorical refusal of many of these patients to return to work—a step which would immediately remedy the allegedly causal economic situation—even when their own doctors have repeatedly urged them to do so and when they are palpably fit for employment by any but their own standards. Thirdly, acceptance of liability for the accident at an early stage in negotiation is rarely if ever followed by recovery, though it reduces the outstanding issue to a simple one of "how much?" Finally, a flood of common-law claims continues despite the basic security afforded by the industrial injury provisions of universal National Insurance.

An alternative explanation of the class gradient relates to the question of social responsibility. It encounters the initial difficulty that little reliable information is available about the social attitudes of these patients before their accidents, and it relies chiefly on the suggestion that the attitude of patients with the established syndrome to work and society is so abnormal that it seems more likely to represent an inherent orientation than merely the symptom of an acquired neurosis. It must be admitted that an egocentric denial of social obligations is not unknown in other forms of chronic psychoneurosis.

The relation of accident neurosis to a lack of social responsibility is supported by its infrequency in workers who take pride in an important job, and its predilection for those human cogs in the industrial machine whose employments afford little opportunity for any kind of satisfaction or self-fulfilment.

Clearly recognizable malingering is rare, but the condition is still more rarely diagnosed. Many of those intimately concerned with compensation work—and I refer here to trade union and insurance officials as well as to judges, barristers, and solicitors—are convinced that it is far from uncommon in these cases, and deplore the inability of doctors to recognize the condition or their hesitancy in expressing an opinion in this connexion to which they will freely admit in private conversation. Except in connexion with criminal offences or in the presence of outspoken psychopathy, accident neurosis is the only context in which frank simulation has been personally encountered on more than a few occasions. It was seen in three of the head injury cases described in the first lecture—a "hysterical" gait which disappeared as soon as the patient left the consulting-room; tell-tale nicotine stains on the fingers of a limb allegedly the site of flaccid paralysis; and a puzzling aphasia after a trivial blow on the head, correctly diagnosed only by the private detective who heard the patient's clarion call for "tea and muffins" ring out across a crowded tearoom within half an hour of an inconclusive consultation. Such instances encourage little confidence in one's ability to recognize similarly motivated simulation in the large majority of cases where the symptomatology is entirely subjective.

Whatever the true position in the case of malingering, gross exaggeration of disability is a common feature of accident neurosis.

Whether such exaggeration is conscious or unconscious is a question often debated between lawyers and psychiatrists in court. To many psychiatrists it presents no problems, and they authenticate the complainant's unawareness of motivation with a confidence that seems impressive—until one reflects that differentiation between conscious and unconscious purpose is quite insusceptible to any form of scientific inquiry, and that it depends on nothing more infallible than one man's assessment of what is probably going on in another man's mind. To me the question is unanswerable in general and answerable only by guesswork in the individual patient. Its implication is, of course, that the unconsciousness or subconsciousness of the mental processes involved is a touchstone of "genuineness" and therefore of compensability. But does this uncertain and arbitrary differentiation merit the central place accorded to it in medico-legal thinking? Whether exaggeration and simulation are "conscious" or "unconscious," their only purpose is to make the observer believe that the disability is greater than it really is. To compensate a man financially because he is stated to be deceiving himself as well as trying to deceive others is strange equity and stranger logic.

Nature of Accident Neurosis

It may be because accident neurosis is more commonly dealt with by orthopaedic surgeons and solicitors than by psychiatrists that it has been the subject of so little systematic psychiatric study; for example, only 7 of the 50 cases followed up here were ever seen by a psychiatrist. It is in textbook contributions rather than in original papers that formal psychiatric appraisals of the disorder must be sought, and with a few outstanding exceptions such a search reveals little that is enlightening or realistic. The studies of neurologists have been more numerous but equally fragmentary.

Most writers accept the consistent relationship of the syndrome to the compensation issue, the hopelessness of treatment, and its usual tendency to recover after settlement—though in the last connexion many psychiatrists make more of the occasional exceptions. In general, neurologists have approached the problem pragmatically, attributing a central aetiological role to the inescapable factor of compensation, and regarding the syndrome as motivated by a hope of financial gain which few of them are prepared to accept as exclusively unconscious. Most psychiatrists have considered such an interpretation too unsubtle, and the relation between

neurosis and compensation as obscure if not actually questionable. Such views lean heavily on the distinction between conscious and unconscious motivation, the difficulties of which have been mentioned.

One such psychiatric interpretation allows a secondary contribution of compensation to the causation of accident neurosis, in that it is supposed to furnish the patient with the leisure and opportunity to "play out" his pre-existing latent emotional conflicts in the form of a nervous illness. This view almost certainly originated under the circumstances of the old Workmen's Compensation Acts, where continuing payments were often made throughout disablement, and it seems even less credible under current conditions, where present financial sacrifice is apparently sustained by nothing more than the hope of ultimate financial redress. Nor is it compatible with the relationship demonstrated between severity of the injury and incidence of neurosis; severer injury would surely afford a more sustained opportunity for the emotional indulgence postulated.

Other psychiatrists stress the aetiological contributions of immature behaviour-patterns, previously suppressed longings for sympathy and attention, or masochistic desires to experience pain and misery. It is difficult to feel that such facile verbalizations do more than describe the patient's symptomatology in terms of the observer's articles of belief. Physicians of the psychoanalytic persuasion, always alive to the emotional significance of money, have accorded it a more important part in the present context, regarding financial compensation as perpetuating disability by the mechanism of "secondary gain." In this way it is allotted a subordinate aetiological role, the primary cause of this as of other neurosis being "avoidance of the Oedipus situation . . . activating one's infantile sado-masochism or one's castration-anxiety, or both" (Fenichel, 1932). Until the victim of accident neurosis struck his head a smart blow on a low beam in the mine he was presumably coping with these knotty problems, at any rate to his own satisfaction.

Some psychiatric conjectures about accident neurosis seem indeed to signify little more than a refusal to concede a connexion between the nervous disorder and the prospect of compensation which is implicit in the facts of the case. Such an attitude may owe something to that addiction to obliquity of thought which is an occupational risk of the psychiatrist's calling, but probably more to a natural reluctance of the mind trained in recognizing deeper motives to the acceptance of a psychopathology so superficial and so banal, however cogently sustained by the natural history of the syndrome.

My formulation of the problem, conceived within the framework of the clinical facts outlined above, is necessarily tentative, and begins indeed with a reservation. For what it is worth as a clinical entity, accident neurosis represents what is left of the nervous sequelae of accidents when other organic complications such as intellectual and personality change and occasional frank psychoses—especially though not exclusively depressive—have been excluded. I would also feel bound to exclude a small but important group of outspoken anxiety states, accompanied by appropriate somatic and autonomic signs, which sometimes follow a terrifying experience. Such syndromes usually affect predisposed subjects, and the general flavour of the case as well as the presence of objective signs and the absence of hysterical features bespeaks an acute psychiatric illness of real severity. Like most such illnesses these usually show a prompt response to treament.

It will be seen that the diagnosis of accident neurosis is not always as easy as may have been suggested above. There is indeed a further complication. In this clinical situation the prognosis of organic deficit, depressive illness, or authentic anxiety state is less predictable than when similar illnesses occur under other conditions: such syndromes may be unduly prolonged and elaborated by the mechanisms which are responsible for accident neurosis itself.

If the clinical findings described above are fairly representative of the problem as a whole—and there is no dearth of clinical material available to confirm or refute them—then it seems clear that accident neurosis is not a function of the accident itself, but of the setting in which this occurred. In my opinion it is not a result of the accident but a concomitant of the compensation situation and a manifestation of the hope of financial gain. The condition is not encountered where this hope does not exist or where it has been finally satisfied or dissipated. There is no feature in the natural history of the disorder which is incompatible with this view, and there are many which can hardly be accounted for by any other. Nevertheless—and despite the rather stereotyped symptomatology of the syndrome, which can reasonably be described as representing the layman's idea of a "nervous breakdown"—accident neurosis is not an entirely homogeneous syndrome, but presents a spectrum ranging from gross conversion hysteria at one end of the scale to frank malingering at the other.

To accept these cases uncritically as instances of hysteria is to concede a general unconsciousness of motivation which strains my credulity. Indeed, what "evidence" is available on this issue points rather in the opposite direction. If the question of financial compensation is tactfully discussed with the subject of accident neurosis its significance is in most instances freely admitted: quite often, indeed, it is revealed as an all-absorbing obsession. Intriguing variants of this common reaction are represented by the patient who begins the consultation with an unsolicited protestation of his utter disinterest in the compensation issue; and by the occasional claimant who avows entire ignorance of the reason for his examination and expresses surprise at its connexion with a claim for damages which had entirely slipped his memory.

Legal Aspects

The legal issues, both of principle and of expediency, involved in a consideration of accident neurosis have been summarized by MacMillan (Buzzard *et al.*, 1928) and more extensively presented in a well-documented review from the United States by Smith and Solomon (1943).

The first and crucial legal question is: Can accident neurosis (or traumatic, compensation, or litigation neurosis, which, as Smith and Solomon point out, are all alternative terms used to describe the same familiar clinical syndrome) reasonably be regarded in law as directly resulting from the accident? From the purely judicial point of view there is nothing special about this question. Such issues of causation are of course "the daily business of the judge . . . to discriminate between those things which were and those things which were not, the direct consequence of a wrong or tort"

(MacMillan). Judges are, of course, equally familiar with the common tendency of litigants to exaggerate the wrong done to them, to introduce illegitimate items of claim, and to extend the hypothesis of causation beyond what is probable and reasonable.

In deciding such issues, two legal principles are often invoked. First, the question of remoteness. The damages claimed as the direct result of an accident must be in respect of the "natural and probable consequences" of the occurrence—an apparently simple concept, but one often difficult of application. If the sequel claimed is too indirect, too remote in time or in the chain of causality, damages may be disallowed. Secondly, the directness of the relationship between occurrence and sequel may be interrupted by what is known in law as a *novus actus interveniens*—the intervention of a new cause operating to produce the end-result: for instance, a motorist liable for fracturing the plaintiff's arm will probably not be held legally responsible for permanent disability which subsequently results from negligent surgery; this amounts to a *novus actus*.

Several arguments of principle have been adduced in favour of regarding accident neurosis as a result of the accident to be accepted and compensated at its face value as relevant cause of disablement. First, it is impossible to maintain that the plaintiff would be in his present condition if there had never been an accident, and therefore, however trivial the physical or mental trauma involved may appear to the observer, it must be accepted as having wreaked disproportionate havoc in this special instance. Secondly, since courts of law, at any rate in Great Britain and the United States, have gradually come to accept as axiomatic the current view that mental suffering is every bit as real and distressing as that which results from physical injury, such suffering is surely equally worthy of financial compensation. Thirdly, whatever predisposition or undue vulnerability of the personality to neurosis may be postulated retrospectively, the employer took his employee, or the bus company its passenger, as it found him, and if this particular employee or passenger develops disabling neurosis after a trivial accident the employer or the company cannot at this late stage evade responsibility by pleading psychoneurotic predisposition in mitigation of damages, any more than by pleading the pre-existence of a thin skull in the case of a fracture.

The legal arguments which have been put forward against the eligibility of the condition for financial compensation have centred chiefly round the question of how far the neurosis can be regarded as a "natural and probable consequence" of the accident. Since such a sequel ensues in only a minority of otherwise similar accidents, and since it usually follows minor injury, it is argued that some other causal factor must be operative, probably some form of constitutional vulnerability. The analogy of the "cracked vase" has been used, in which a previously invisible fault begins to leak water after an insignificant impact, and it is suggested that, since the accident can be held only partly responsible for such a sequel, the condition cannot logically or equitably be regarded as compensable in its entirety, and that the defendant should only be held responsible for such disability as a normal person might be expected to suffer as a result of a similar occurrence. Where previous neurotic disability or evidence of significant predisposition can be proved such a view seems often to be tacitly accepted in court; but we have seen that no such evidence is found in more than half the cases under consideration, and the courts show a natural reluctance to accept a "crack in the vase" which is merely inferential.

There is, however, another serious practical difficulty involved in compensating neurosis, which is unrelated to the more theoretical questions of aetiology. In assessing the nature and severity of such a disability the assessor—whether medical or judicial—is almost entirely dependent on the patient's own description of his subjective sufferings, and even in the last resort on his own assessment of their severity. Minimization of symptoms is by no means unknown after serious injury—for example, to the brain—but it is rare in any form of psychoneurosis, and its presence has certainly never been described as a feature of the condition under discussion. Indeed, in these cases, where the patient is engaged in making out a case for proportionate financial redress, some degree of exaggeration of disability might be regarded as no more than an anticipated human failing. That such a plaintiff is also the main witness regarding the degree of disability is clearly paradoxical; it precludes any objective basis for judicial assessment, and renders this almost entirely dependent on subjective considerations.

Since these disproportionate results of trivial injury are not seen except where financial compensation is in question, since they are often claimed by subjects in whom there is no evidence of special psychiatric vulnerability, and since there has often been an appreciable latent period between the accident and the onset of nervous symptoms, it is perhaps surprising that the doctrines of remoteness and of the *novus actus interveniens* (in this instance the hope of compensation) have not more often been invoked in trial of such cases.

In general, however, the law favours the plaintiff. Most cases are settled, and no claim is too ludicrous to lack a certain nuisance value in cash. Once in court the judicial assessment sometimes seems to be based on little more than the axiom that but for the accident the man would not have been in his present condition—a statement unexceptionable in itself, but a convenient oversimplification of a complicated relationship. Its acceptance implies that subsequent absence from work must also be regarded as fully attributable to the accident—though to the doctor it may clearly be disinclination rather than incapacity which automatically pushes up the "special damages" by a thousand pounds.

But this is only one of many discrepancies between the approaches of the doctor and of the lawyer in this common field. In the matter of aetiology, for example, the doctor is unwilling to commit himself categorically without objective evidence, and even then his answer can rarely be couched in the "either-or" terms inevitably demanded as the basis of a clear-cut judicial decision: on the other hand, the more realistic concept of multiple causation is difficult to translate into terms of legal settlement. Again, doctor and lawyer are sometimes at cross-purposes over the question of settlement, the lawyer insisting that there should be no settlement without clinical finality, the doctor that there can be no clinical finality without settlement.

Prevention

That the situation outlined above is unsatisfactory goes without saying. Despite the millions of words that have been written on the subject, the nature of psycho-

neurosis remains obscure, but in a general sense there would be wide agreement that hysteria at any rate represents some form of biological protection against stress or danger—an escape from or a protection against reality. Without prejudice to the vexed issue of conscious or unconscious motivation, it must be conceded that to endow such a condition with the added attraction of secondary financial gain is to ask for its persistence for as long as it yields benefit—which in my view is exactly what happens in the syndrome under consideration. That a disability motivated by the hope of financial gain is regularly thus rewarded can hardly be considered desirable from any point of view. Nevertheless it is much easier to see what is wrong than how to remedy it.

The function of the trade union official is to pursue what he regards as his member's interest; that of the solicitor to press his client's case, such as it is, to the best of his ability. It would be unrealistic to hope that either will discourage compensation claims for neurosis, all but the most outrageous of which will end in some degree of pecuniary benefit to the party he represents. The conscientious doctor who tries to keep his patient at work despite his minor injury is pitting himself single-handed against powerful social and economic forces all of which press in the opposite direction. It seems certain that effective prevention would demand far-reaching social readjustments rather than purely medical measures.

It is said, for example, that some large business concerns in the United States have successfully employed a system of rehabilitation through work rather than compensation, the injured worker being provided with first-class medical treatment and drawing his pre-accident earnings while he is nursed back through an early return to light duties and gradually to his old job. A somewhat similar approach characterizes the management of industrial injuries in Communist countries, and it clearly has much to recommend it. In Britain and elsewhere, however, it encounters the immediate difficulty that the widespread application of the insurance principle absolves the employer from his direct responsibility for the injured workman, and that he is under little obligation to find any interim employment for a man who is now the insurance company's liability. There seems to be little doubt that in certain industries this shifting of responsibility militates similarly against the general adoption of effective but expensive measures for the prevention of accidents.

From a purely medical point of view a strong case can be made out for regarding neurosis as a non-compensable disability. For practical purposes this appears to be the position in France, but, however justifiable such a step might appear from the point of view of social prophylaxis, the chances of its legal acceptance in Great Britain seem slender. Not only would it make compensation crucially dependent on a diagnostic differentiation between psychoneurosis and psychosis—a field in which not even the most expert would claim infallibility; it would also imply the unconditional rejection of a number of claims which would be fairly generally regarded as perfectly genuine.

Mention must be made of the marked improvement in the situation with regard to industrial injury which has followed the supersession of the old Workmen's Compensation Acts by the industrial injuries provisions of the National Insurance Act of 1946. Under the new Act, medical assessment has been vested in medical boards (composed of experienced doctors usually also engaged in independent practice) and, on appeal, in medical appeal tribunals (constituted by senior consultant surgeons and physicians sitting under the chairmanship of an experienced lawyer). In difficult cases either body can request examination by an independent specialist. This arrangement has greatly reduced the delay and expense inseparable from the more formal legal proceedings by which such cases used to be dealt with in the county courts, and it appears to be reasonably satisfactory to all parties concerned.

The fact that disablement caused by industrial injury is compensated at a higher rate than that resulting from illness is a relic of the old Act which seems hardly logical under present circumstances, and this is probably the main cause of a large number of pettifogging claims for trivial injuries which are also encouraged by the ease and informality of procedure. Such claims are, however, easily disposed of. The inclusion of psychiatric with physical sequelae of injury in the assessment of disability is specifically allowed for under the Act. However, a procedure in which doctors rather than lawyers play a major part in assessing disability has led to a reduction both in the number and in the monetary value of awards for functional nervous disorders. Indeed, it is my experience that severe disability from accident neurosis is hardly ever encountered in these instances unless there is a concurrent claim at Common Law.

Why can this efficient and economical arrangement not be extended to cover the minority of industrial injury claims which are still sent to the courts to be dealt with under Common Law, because of an allegation of negligence or failure to observe a statutory obligation? The first reason for this is that the medical aspect of such cases is often overshadowed by other features which may involve complex technical and legal problems quite beyond the competence of a medical tribunal. Secondly, damages in Common Law are final and irrevocable lump-sum settlements, which cannot subsequently be revised in relation to the patient's condition, as can pensions paid under the National Insurance Scheme. Such damages must take account of social and domestic factors independent of the purely clinical issue of disability—to say nothing of the financial evaluation of pain and suffering. Finally, while it may be questionable how far the average plaintiff himself would resent being deprived of the full panoply of trial by an assize judge, it is unlikely that the legal profession would willingly relinquish more of its traditional responsibility to yet another administrative body.

The frequently made recommendation that the judge in such cases should sit with a medical assessor to advise him also has obvious attractions, but it is open to similar criticism. Most medical experts would certainly prefer to be called as witnesses by the court, instead of on behalf of the plaintiff or the defendant. On the other hand, few would relish a situation which arbitrarily elevated one of their number to a quasi-judicial capacity. There is no certainty in medicine, and with all its faults the judge's weighing of evidence brought out by cross-examination of two experts, often of somewhat different outlooks, is less likely to leave relevant medical considerations undisclosed and arguments unheard than a statement of opinion by a single expert, however authoritative.

There is, however, one measure which I would strongly urge as certain to affect an appreciable reduction in the

human and economic wastage inherent in the present situation, and one which would almost certainly be widely acceptable. There can be little doubt that the law's delays are a potent factor in increasing the total sum of disablement caused by accident neurosis, and that a separate trial of the issue of liability within six months of the accident would minimize its effects, at any rate in those cases where liability is not proved. Equally the medical issues involved should be similarly decided once and for all at the end of a rather longer but fixed interval of time. From a medical point of view the patient's interests are certainly better served by an early settlement than by one that is delayed, even though delay may imply some degree of financial advantage.

What the doctor himself can do is limited. It is clearly incumbent on him to encourage a robust attitude to minor injury. Although accident neurosis is a motivated illness, its occurrence is far from invariable even where the motivational background is consistent, and there can be no doubt that the "tough" person is less likely to claim. This may be in part because he does not develop the minor neurotic nucleus around which the predisposed subject builds his edifice of disability, but we have seen that predisposition is far from invariable, and the influence of social attitudes is almost certainly more potent.

There are many middle-class patients who sustain real physical injuries under conditions which would thoroughly justify claims for compensation, but who flatly refuse to claim. They may press most vigorously for restitution of damage to their cars, and may indeed exhibit a remarkable lack of scruple in describing the condition of the vehicle before the accident—but they feel that to make a fuss of minor personal disability or to attempt to turn it to financial advantage represents a socially unacceptable standard of behaviour.

It has been argued that the "toughness" of the injured steeplechaser, in contrast to the "tenderness" (in the Jamesian sense) of the injured workman, is innate. This deterministic view can hardly be wholly applicable in a fluid society. Genetic or early influences no doubt play a part in determining such patterns of behaviour, but these are predominantly cultural, and vastly affected by environment and example, as, for instance, of school or regiment. I have been struck by a group of patients, not predisposed to neurosis, who had survived the hazards of operational war service psychiatrically unscathed, but who broke down with gross hysterical disability after minor injuries sustained under industrial conditions where serious risk was remote. Why had these patients not succumbed with a hysterical reaction to the infinitely more stressful circumstances of aircrew, tank, or submarine service? Age and the acquisition of family responsibilities may have played a part, but it is also true that while such breakdown under Service conditions would have achieved its primary purpose of ensuring the withdrawal of its victim from danger, it was socially unacceptable, and implied rejection from the group of which he was a member. Incidentally it would also have involved financial sacrifice rather than the possibility of financial gain. Neither disadvantage obtains under current industrial conditions.

Conclusions

Like its causation, the prevention of accident neurosis can be realistically conceived only in social terms. Consideration of its epidemiology and clinical features allows little doubt that the condition could be prevented, and its prevention would certainly make a significant contribution to the national economy. But the minor measures discussed above would hardly do more than scratch the surface of a problem which is more properly the concern of politics than of medicine. A Milroy lecturer need make no apology—and may perhaps even be excused the customary invocation of Virchow—if he seeks in conclusion to outline his own tentative view of the aetiological background of the syndrome in political terms.

To say that our society is in a state of transition is to utter a platitude. All societies have always been in states of transition. That the conflicts between different concepts of social organization seem especially acute in our own day may be due to nothing more than the fact that they are close at hand. In any case, however, they constitute powerful determinants of human behaviour, and in my view their operation is clearly evident in the clinical situation under discussion.

In practically every civilized country the past half-century has witnessed the socialization of considerable sections of economic and public activity. The process has been uneven. In some countries this development has occurred explosively and more or less completely, in others piecemeal. Among countries not formally committed to Socialism, Britain lies to the left of centre in a spectrum which has the United States at one end and some of the Scandinavian countries at the other. In Britain large sections of public activity are fully socialized. Side by side with such developments, however, the institutions and many of the attitudes of capitalism persist—to say nothing of those archaic but virile remnants of feudalism which intrigue many foreign visitors to our country.

Our present fluid social compromise of welfare capitalism includes a comprehensive scheme of insurance which afford the sick or injured workman and his family a degree of financial security comparable with that which obtains in most Socialist countries. What our society has signally failed to provide are the industrial discipline which is inherent in Socialism, or the industrial morale to which it aspires. The average industrial worker—and here I literally mean the average worker and not a member of the politically sophisticated minority—either turns a deaf ear to the perennial pleas of politicians and leader-writers for "a sense of partnership in industry," or for "co-operation in management," or regards them with frank and sometimes even ribald cynicism. Unconvinced that a wider distribution of consumer goods has changed the basic structure of society, he continues to nourish a strong awareness of the antithesis between "us" and "them," between worker and employer (with whom salaried management above a certain level is tacitly equated). It is fashionable to deprecate the role of such class antagonisms in contemporary society, but a glance at the recent history of labour relations in several of our more prosperous industries lends little support to such complacency.

This, then, is the social setting in which accident neurosis flourishes. The exploitation of his injury represents one of the few weapons available to the unskilled worker to acquire a larger share—or indeed a share of any kind—in the national capital. Its possible yield may not bear comparison with the weekly recurring fantasy of a win in the pools, but it is more clearly within his grasp, and it may yet endow him with a

capital sum such as he could never have saved during a lifetime of unremitting labour. The employer or his representative, the insurance company, is fair game. To question the moral issues of the situation would seem hardly more relevant to the claimant than to argue the ethics of unearned income, capital appreciation, or the take-over bid—phenomena which manifest the operation of similar motives at other levels of what he accepts without question as a ruthlessly acquisitive society.

How far has the socialization of large sectors of our economy influenced this situation and these attitudes? It can be said with some confidence, for example, that nationalization of the industry has radically affected the orientation of the coal-miner to his employing organization. The hatred of the miner for the coal-owner had its roots deep in history, and was felt with a passion unknown in other fields of industry. The miner of to-day grumbles with his fellows about bureaucracy, but he will defend the Coal Board vehemently against outside criticism. I think it would be an exaggeration to claim that he feels a close sense of identification with it. The chain of command is still too indirect for such identification to permeate the lowest levels of the industry. Nevertheless, the miner of to-day feels that in general the Board's interests are his own and that in the last resort their collaboration is vital to the survival of the industry and of the curiously individual pattern of society which it sustains.

The conception of accident neurosis outlined in these lectures would be strengthened if it were possible to claim that the incidence of the condition had been reduced by this change of ownership and attitude in the coal industry. No figures are available in this connexion, but the attitudes of the injured miner in the matter of claims for compensation do not appear to differ in any obvious way from those of workers employed by the larger private firms. Like other nationalized industries the Coal Board runs its own insurance scheme, generously administered and continuing a long tradition of settling nearly every case round the conference table. It is my impression that this scheme works better than where the responsibility has been handed over to an insurance company. Within the limitations of the industry, management makes great efforts to furnish light employment as soon as practicable, medical referees are often asked to adjudicate on conflicting medical reports, and the inevitable delays of litigation are avoided. But the successful operation of the scheme owes more to the responsibility of the men's representatives than to that of the claimants themselves. The best of these are men of the highest calibre and integrity who have spent a lifetime in the industry and who have too great a sense of social responsibility to have any patience with dishonesty or exaggeration.

If such information were available a third lecture could be written on the epidemiology of accident neurosis and its differential incidence in countries with different forms of political, judicial, and administrative organization. Personal experience suggests, for example, that it is probably a less conspicuous and ubiquitous problem in Eastern than in Western Europe. But he would be a bold man who ascribed any such apparent reduction in incidence to a change in ethos, rather than to the deliberate formulation of administrative policies which have rendered the disorder unprofitable and therefore without purpose.

I thank the patients, solicitors, and insurance companies who so generously gave of their time and trouble to ensure the completion of the clinical data; and my friends of the Bench and the Bar who have—I hope—purged my contribution of legal solecisms.

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A STUDY OF THE ANDROGENIC AND SOME RELATED EFFECTS OF METHANDIENONE

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Testosterone derivatives, apart from their virilizing action, may have, to a varying extent, any of the following effects (Dorfman and Shipley, 1956). (1) They may be anabolic, promoting nitrogen retention (in the form of protein) and muscle and organ growth. (2) They may depress other endocrine glands, and, for example, interfere with the oestrous cycle in women and depress spermatogenesis in men. (3) They may have a progestational effect. (4) They may cause salt and water retention. (5) They may inhibit the growth of cancer of the breast in females, and may increase the rate of growth of cancer of the prostate. (6) Some of the synthetic analogues of testosterone—namely, those with an alkyl group in the 17α position—may adversely affect liver function (Foss and Simpson, 1959; Wynn *et al.*, 1961).

The anabolic effect of the derivatives of testosterone may be of considerable clinical value in the treatment of certain wasting illnesses and senile and post-menopausal osteoporosis. They have also been used to counter the catabolic effects of long-term corticosteroid therapy. A most important application is in the treatment of breast cancer. In most of the conditions mentioned prolonged treatment with these steroids is required. It is therefore an advantage if the drug can be given by mouth rather than by injection. Unless the drugs are to be used for the treatment of

hypogonadism in males, there is also an advantage in using a compound which retains the anabolic effects of testosterone but has minimal virilizing action. Such a compound is methandienone.

Methandienone (1-dehydro-17α-methyltestosterone; "dianabol") is very similar in structure to methyltestosterone, differing only in the presence of a double bond between carbon 1 and 2 in the A ring of the steroid nucleus. It is active when given by mouth. Desaulles *et al.* (1959) found that in the rat it was as powerful an anabolic steroid as testosterone propionate or methyltestosterone, but had little of the androgenic action of these latter two steroids.

We have studied the metabolic effects of methandienone, and have found that it has a powerful anabolic action. We hope to report these studies separately. It

TABLE I.—*Clinical Details of Seven Pre-menopausal Women Given Methandienone*

Case No.	Age	Diagnosis	Dose and Duration of Methandienone Therapy (mg./Day)	Acne	Hair			Voice	Libido	Musculature	Defeminization	Ext. Genitalia	Sense of Well-Being	Effect on Menses
					Scalp	Face	Body							
4	37	Renal tubular acidosis with nephrocalcinosis	25 for 200 days*	−	−	−	−	−	−	−	−	−	−	Regular periods till start of methandienone. None since being on drug
7	28	Severe Raynaud's disease	20 for 210 days*	−	−	−	−	−	++	−	−	−	−	Regular periods till start of methandienone. One short period after 20 days on drug. None since
13	26	Septic abortion. Acute tubular necrosis. Cachexia	25 for 22 days	++	−	−	−	−	−	−	−	−	+	No periods since septic abortion two months prior to methandienone therapy
29	39	Anorexia nervosa	20 for 16 days	−	−	−	−	−	+	−	−	−	−	No periods for 18 months prior to methandienone. First normal period after 10 days on drug
30	26	,, ,,	20 for 10 days, then 15 for 10 days, 10 for 8 days, and 5 for 6 days	−	−	−	−	−	−	+	−	−	−	No periods for 5 years prior to methandienone therapy
31	44	Severe asthma on triamcinolone	50 for 14 days, then 25 for 82 days*	+	−	+	−	−	−	−	−	−	+	Regular periods till start of methandienone, one normal period after 8 days on drug. None since
32	52	Chronic bronchitis and asthma on triamcinolone	25 for 100 days*	++	−	−	−	−	−	+	−	−	+	Regular periods till start of methandienone. None since being on drug

* Still on methandrienone at time of completing present study.

TABLE II.—*Clinical Details of* 12 *Post-menopausal Women Given Methandienone*

Case No.	Age	Diagnosis	Dose and Duration of Methandienone Therapy (mg./day)	Acne	Sebaceous Secretion	Hair			Voice	Libido	Musculature	Defeminization	Ext. Genitalia	Sense of Well-being	Effect on Menopausal Symptoms, if Present
						Scalp	Face	Body							
1	60	Acute intermittent porphyria. Post-menopausal osteoporosis	50 for 33 days, then 25 for 160 days*	−	−	−	−	−	−	−	−	−	−	++	None present
3	50	Acute glomerulonephritis. Cachexia	25 for 70 days	−	−	−	−	−	±	++	++	+	−	++	Severe menopausal symptoms completely stopped while on methandienone
5	28	Cushing's syndrome. Peptic ulceration	50 for 27 days, then 100 for 12 days, 50 for 12 days, 12·5 for 29 days, and 30 for 130 days	++	−	−	±	−	−	−	+	−	−	++	Mild menopausal symptoms stopped while on methandienone
6	60	Systemic lupus erythematosis on prednisone. K⁺-losing pyelonephritis. Cachexia	50 for 40 days, then 12·5 for 80 days, and 25 for 40 days	−	−	−	−	−	−	−	++	+	−	+	None present
9	43	Severe pyelonephritis. Anorexia nervosa	25 for 260 days*	−	−	−	−	−	−	−	−	−	−	+	,, ,,
10	75	Post-gastrectomy diarrhoea. Malnutrition	25 for 33 days and 201 days*	−	−	−	−	−	−	−	++	−	−	++	,, ,,
11	51	Chronic pyelonephritis. Malnutrition	50 for 7 days, then 25 for 44 days	+	+	−	−	−	−	−	+	+	−	+	Moderate menopausal symptoms stopped while on methandienone
15	62	Carcinoma of breast with bone and liver metastases	25 for 10 days	−	−	−	−	−	−	−	−	−	−	−	None present
16	37	Cushing's syndrome. Carcinoma of adrenal cortex with liver metastases	50 for 10 days	−	−	±	±	−	−	−	−	−	−	−	,, ,,
17	47	Chronic bronchitis and asthma on prednisone	50 for 43 days, then 25 for 60 days*	+	−	−	−	−	−	−	+	−	−	++	Mild menopausal symptoms stopped while on methandienone
19	83	Ischaemic peripheral arterial disease. Malnutrition	50 for 41 days	−	−	−	−	−	−	−	+	−	−	++	None present
26	52	Post-gastrectomy abdominal fistula. Cachexia	50 for 96 days	+	+	+	−	+	+	−	++	+	−	++	,, ,,

* Still on methandienone at time of completing present study.

was considered important to verify the dissociation of the anabolic from the androgenic effects of methandienone in man. We report here our experiences of (*a*) the androgenic effect of methandienone, (*b*) the effect of methandienone on menstruation, (*c*) the effect of methandienone on menopausal symptoms, and (*d*) the psychological effects of methandienone.

Case Material.—We have divided the patients into three groups—namely, pre-menopausal women (7 cases), post-menopausal women (12 cases), and adult males (11 cases). The clinical details of these cases are summarized in Tables I, II, and III.

Androgenic Effect of Methandienone

The following possible evidence of an androgenic action was looked for in the female patients: acne and increased sebaceous secretion of the face and scalp, tendency to loss or thinning of scalp hair, increase in facial or body hair, increase in musculature, increase in libido, changes in the pitch of the voice, and changes in the external genitalia or evidence of defeminization.

It is recognized that some of these changes—for example, increase in musculature and in libido—would be at least partly attributable to the anabolic action of the drug, as opposed to a specific virilizing action.

Acne and Increase in Sebaceous Secretion

Severe acne was not a common complication of treatment with methandienone. Of the 12 post-menopausal women, four developed acne. In Case 11 there was a mild acneiform eruption around the mouth, chin, and forehead after 40 days on methandienone (25 mg. a day). In this patient there was also an increase in greasiness of the scalp and face. In Case 26 50 mg. of methandienone a day was given for 96 days; there was a similar acneiform eruption on the face, also associated with increased sebaceous secretion, after the patient had been on 50 mg. of methandienone for a continuous period of 70 days. In Case 5, a patient suffering from Cushing's syndrome with mild virilizing symptoms (loss of scalp hair, increased facial hair), a very marked acneiform rash involving the whole of the back developed after she had been on a very prolonged course of methandienone. At the time the rash developed the patient was receiving only 12.5 mg. of methandienone a day. Subsequently this dose was increased to 30 mg. and continued for another 130 days. Despite this increase in dosage the acne responded rapidly to local treatment with resorcin and sulphur, and it did not recur subsequently. In Case 17 there was a minimal acneiform eruption of the back after 25 mg. of methandienone daily for 30 days. This has subsequently started to clear despite continuation of the drug.

Of the seven pre-menopausal women, three developed acne. In Case 13 this was an extremely pustular form of acne, involving the forehead, which came on suddenly after the patient had been receiving 25 mg. of the drug daily for 22 days. This patient had diminished renal function, and at the time of the appearance of the eruption was running a higher fever—101–103° F. (38.3–39.4° C.)—from a severe pelvic infection. Methandienone therapy was stopped and the rash cleared within 12 days, leaving minimal scarring. Cases 31 and 32, both on prolonged corticoid therapy for severe asthma, developed acne while on methandienone. This mainly involved the back, there being no visible eruption on the face.

Changes in Scalp Hair.—In the seven pre-menopausal women no change in scalp hair was noticed while on the drug. Of the twelve post-menopausal women only one (Case 26) complained of thinning of the scalp hair, with more coming away on the comb. This occurred after she had been having 50 mg. of methandienone daily for two months. Cases 5 and 16 already had marked thinning of the scalp hair due to Cushing's syndrome, and in Case 5 the hair actually became thicker and less fragile while on methandienone.

Increase in Facial or Body Hair.—In only three patients was any increase in facial hair noticeable. In two of these (Cases 5 and 16) facial hirsuties was already present due to Cushing's syndrome, and the slight increase noted cannot with certainty be attributed to methandienone. Similarly in Case 31 the patient had had facial hirsuties prior to starting the drug, probably associated with the high corticoid doses she was being given for severe asthma. Although she did not notice any increase in this hirsutism while on methandienone, it was apparent to the medical staff.

Increase in Musculature.—It is difficult to know how much reliance can be placed on this as a sign of virilization, as it is primarily a result of anabolism. Many cases exhibited some increase in muscle mass and in muscle power while on the drug. In the pre-menopausal group of women no case exhibited this to any marked extent. In the post-menopausal group it occurred in several cases, being most marked in Cases 3, 6, 10, and 26. Only in Case 3 was this of any embarrassment; the patient felt that it was making her rather male-like.

TABLE III.—*Clinical Details of* 11 *Male Patients on Methandienone*

Case No.	Age	Diagnosis	Dose and Duration of Methandienone Therapy (mg./day)	Acne	Sebaceous Secretion	Hair			Libido	Musculature	Sense of Well-being
						Scalp	Face	Body			
2	28	Acute idiopathic osteoporosis	100 for 26 days, then 75 for 198 days	+	+	±	−	−	+	+	++
8	53	Pancreatic steatorrhoea malnutrition	50 for 65 days*	−	−	−	−	−	−	+	++
12	21	Idiopathic hypercalciuria	50 ,, 14 days	−	−	−	−	−	++	−	−
18	24	,, ,,	50 ,, 10 ,,	−	−	−	−	−	+	−	−
20	70	Prostatic enlargement. Pyelonephritis. Cachexia	100 for 6 days, then 50 for 19 days	−	−	−	−	−	−	+	++
22	28	Addison's disease	25 for 8 days, then 8 days off and then 25 mg. for 8 days	−	−	−	−	−	−	−	−
23	30	Idiopathic steatorrhoea. Malnutrition	50 for 98 days*	−	−	−	−	−	−	++	++
24	21	Cushing's syndrome	100 for 22 days	−	−	+	−	−	−	+	+
25	30	Perforated peptic ulcer. Peritonitis. Intestinal fistula. Cachexia	100 for 11 days, then 50 for 15 days, and 25 for 7 days	−	−	+	−	−	−	+	++
27	16	Chronic pyelonephritis with renal failure	100 for 2 days, then 50 for 32 days	−	−	−	−	−	−	−	+
28	14	Anorexia nervosa	10 for 8 days, then 15 for 12 days, and 20 for 6 days	−	−	−	−	−	−	−	−

* Still on methandienone at time of completing present study.

Increase in Libido.—Increase in libido was a prominent symptom of methandienone therapy in two cases. It occurred quite early on in the course of the treatment, within the first week. It occurred in one of the seven pre-menopausal women (Case 7) and in one of the 12 post-menopausal women (Case 3). In Case 7 the effect on libido decreased after about four weeks and was absent after about eight weeks.

Increased libido would seem to indicate some androgenic property of methandienone. However, the control of libido is a complex subject, dependent as it is on psychological and other factors, apart from the androgens. It could in part be explained by the sense of well-being which the drug imparts and the anabolic action of the drug. The increase in libido did not occur in patients over 50.

Change in Pitch of Voice.—Deepening or huskiness of the voice would be expected in those women on a long course of methandienone if the drug had any marked androgenic properties. In fact, in no case did any change in the voice occur, with the possible exception of Case 3, who at times had slight huskiness. Both she and her husband, however, thought that this had been present for many years and was not influenced by the drug.

Evidence of Defeminization, or Change in External Genitalia.—Four patients (Cases 3, 6, 11, and 26) had a facial appearance that was rather more masculine while on the drug. This is difficult to describe, but consisted of increased prominence of the facial bones, loss of the smooth facial contours, and a tendency for increased plethora of the cheeks. Only in Case 3, combined with her increased musculature, did the patient comment on this defeminization. In no case was it so obvious as to be noticed by husband or friends. In none of the patients was there any noticeable atrophy of breast tissue or loss of female body configuration. Changes in the external genitalia were not directly looked for in the female patients. None of the female patients themselves, however, noticed any changes in their external genitalia when they were questioned about this.

Effect of Methandienone on Male Patients

No drug can be said to be virilizing in respect of a male after puberty unless the male has absence of normal testicular function. It is thus difficult to label certain of the actions of methandienone in men.

Of the 11 male patients, only one (Case 2) developed acne and increased sebaceous secretion. In this patient it did not occur until after 200 days of continuous treatment with a very high dosage of the drug (75–100 mg. daily). The acne was of minimal degree, involving the back and shoulders. It was not pustular and did not necessitate treatment.

Only three men (Cases 2, 24, and 25) considered that there might have been thinning of the scalp hair while on the drug. Case 2 had, however, had this thinning of the scalp hair prior to starting methandienone, and he was not certain whether the drug had caused it to increase in extent and severity. The other two patients (Cases 24 and 25) were quite certain that methandienone had caused thinning of the scalp hair, although clinically this was not obvious.

None of the male patients noticed any change in the amount or texture of their facial or body hair while on the drug, and none had to shave more frequently.

Three men noticed an increase in libido while on methandienone (Cases 2, 12, and 18), consisting in increased sex awareness and increase in the frequency of erections and nocturnal emissions. In addition, the patient with Cushing's syndrome (Case 24) commented that his libido had returned to its pre-disease level while on methandienone.

Prostatic hypertrophy is usually a contraindication to the giving of testosterone derivatives, as the androgens act preferentially to cause further prostatomegaly, with the risk of acute urinary retention. It is therefore of interest that Case 20, a patient suffering from prostatomegaly, had no increase in prostatic symptoms although he was given 100 mg. of methandienone daily for six days, followed by 50 mg. daily for 19 days. He was admitted to hospital with a ruptured appendix, after which he had peritonitis and paralytic ileus. He ran a prolonged fever and became greatly wasted. The improvement in his general condition produced by the drug enabled a prostatectomy to be carried out with safety.

Effect of Methandienone on Menstruation

Of the seven pre-menopausal patients, two (Cases 13 and 30) were not having periods at the time of starting methandienone. One (Case 13) had had no periods since a septic abortion two months prior to her course of methandienone. Two months after stopping the drug her menstrual periods restarted and since then have been regular. The other (Case 30), with severe anorexia nervosa, had had amenorrhoea for the five years prior to admission to hospital. Her menses did not recommence during the giving of methandienone nor in the subsequent two months.

Case 29 also had anorexia nervosa, with gross wasting and amenorrhoea for the 18 months prior to her admission. In hospital on a high-protein, high-calorie diet, she rapidly gained weight and was in strong positive nitrogen balance. Menstruation recommenced 23 days after admission, despite her being given 20 mg. of methandienone daily for 10 days before her periods started.

The remaining four pre-menopausal patients (Cases 4, 7, 31, and 32) all had normal and regular menstrual periods prior to being started on methandienone. Cases 4 and 32 have had amenorrhoea since taking the drug (25 mg. daily for 200 and 100 days respectively).

Case 7 had one menstrual period of two days' duration with minimal loss after she had been on methandienone (20 mg. daily) for 20 days. In the subsequent 190 days of methandienone therapy she has had no further periods.

Case 31 had one normal period eight days after starting on triamcinolone (6 mg. daily) and methandienone (50 mg. daily). She has had no further menses in the subsequent 82 days of therapy, despite the dose of triamcinolone and methandienone being lowered to 2 mg. daily and 25 mg. daily respectively.

One of the post-menopausal women (Case 3) is of interest in the present connexion. This patient, aged 50, had had no periods for the two years prior to starting methandienone. During the last week of a 70-day course of the drug (25 mg. daily) there was slight loss of blood lasting two days. A dilatation and curettage at this time showed a smooth endometrial surface, and no scrapings could be obtained. The vaginal "spotting" had ceased before discontinuing methandienone. Ten

days after stopping the drug the patient had an apparently normal menstrual period, followed by a second period four weeks later. Since then there has been amenorrhoea.

None of the other post-menopausal women had any vaginal bleeding while on methandienone or after the drug was stopped.

Effect of Methandienone on Menopausal Symptoms

Four of the 12 post-menopausal women in the present study were complaining, to a variable degree, of symptoms attributable to the menopause. In these patients, as well as in three others with menopausal symptoms who have been seen by us but who are not included in the present series, methandienone rapidly stopped these symptoms.

During the two years when Case 3 had no periods she had been having frequent episodes of flushing and perspiring three or four times daily, each episode lasting about five minutes. At times she also felt rather depressed and had occipital "tension headaches." After the first three days on methandienone therapy the episodes of flushing and perspiring stopped, and did not recur during the 70 days on which the drug was given. As mentioned in the previous section, this patient had slight vaginal "spotting" during the final week of methandienone administration, a diagnostic dilatation and curettage at that time showing a smooth endometrial surface. In the 10 weeks after stopping the drug she had two apparently normal periods. It was only after this that her menopausal symptoms returned; these have persisted ever since, associated with amenorrhoea.

Case 5 had had occasional flushing for two years prior to admission. These stopped after the second week of methandienone and did not recur during the 210 days the drug was given. They began again, however, five days after stopping the drug.

Cases 11 and 17 had had moderate and mild menopausal symptoms respectively in the two years prior to admission. These consisted of flushing, redness and perspiration, and occipital headaches. These symptoms stopped when methandienone was given.

Apart from the slight bleeding seen in Case 3, no other post-menopausal patients had vaginal bleeding while on methandienone or immediately after stopping the drug.

Psychological Effects of Methandienone

An increased feeling of confidence with a sense of well-being was one of the most prominent changes that occurred in several of the patients while on methandienone. It was often remarked on, not only by the patients but by the nursing staff.

The psychological effects consisted of a brighter mental outlook, of a feeling that they could cope with their disease, and of feeling stronger and more confident; they were also associated with an increased appetite. This feeling of well-being was especially notable and of the greatest therapeutic value in the elderly patients with chronic illness—in such patients the results with methandienone were best summed up by the ward sister's remark, "They feel that they can deal with their illnesses as they would have done when they were young and healthy."

Methandienone had no psychological effects on those patients whose illnesses did not produce symptoms of ill-health. For example, it had no effect psychologically on three patients (Cases 4, 12, and 18) to whom methandienone was given to lower the urinary calcium. Three patients with anorexia nervosa (Cases 28, 29, and 30) on a high-calorie high-protein diet were in positive nitrogen balance, were gaining weight, and felt well at the time methandienone was started, and in these three cases it also had no psychological effects. Case 7, apart from her severe Raynaud's disease, felt well at the time of being given the drug, and again no psychological effects resulted.

Three patients who were chronically ill derived no psychological benefit from methandienone. In Case 22, with Addison's disease, the drug produced neither a physical nor a psychological effect. The other two (Cases 15 and 16) who showed no improvement in outlook or well-being suffered from carcinoma with multiple secondaries and had only a relatively short course of methandienone (25 and 50 mg. daily for 10 days respectively). It is of interest that, despite the absence of mental improvement, the drug induced a strong anabolic phase in both, as evidenced by their nitrogen balance.

An increased sense of well-being occurred in 19 of the 30 patients in the present study, usually within the first week of methandienone therapy. Among the seven pre-menopausal women it was a feature in Cases 13, 31, and 32, the latter two of whom had severe asthma and were on long-term corticoid therapy.

An increased sense of well-being occurred in 10 of the 12 post-menopausal patients. In particular it was the older patient who found the greatest psychological benefit from the drug. Two patients, aged 75 and 83 (Cases 10 and 19), rapidly felt much better once on methandienone.

Of the male patients it was again the older patients or the more severely ill in whom the psychological benefit of methandienone was most obvious. Case 20, aged 70, made a rapid physical and mental improvement while on the drug; while Case 8, who prior to methandienone was quite exceptionally uncooperative, unhelpful, and also depressed, once on the drug underwent a marked personality change, felt that he was going to get better, and became reasonably pleasant and easy to nurse.

Discussion

It is likely that any anabolic steroid that is a derivative of testosterone will have some androgenic effect if it is given in a high dosage for a prolonged period.

In rats methandienone has an anabolic effect as great as or greater than other anabolic steroids, such as testosterone propionate, methyltestosterone, norethandrolone, and norandrostenolone phenylpropionate (Desaulles *et al.*, 1959). In nitrogen balances carried out on 16 patients in the present study we found methandienone to have a powerful anabolic effect.

In studies on the castrated rat, Desaulles *et al.* (1959) found it to have approximately one-hundredth the androgenic effect of testosterone propionate, and one-seventeenth the androgenic effect of norethandrolone. With the capon-comb test its androgenic effect was even less.

Foss (1960) found no evidence of androgenic activity of the drug in four women, even when doses of up to 1.6 mg./kg./day were employed for periods of up to 29 weeks. With doses in excess of 0.5 mg./kg./day in children, however, some evidence of androgenic effects was observed.

In the present study methandienone did not appear to have any marked virilizing side-effects, if one excludes those patients who had high levels of endogenous or exogenous corticoids. Acne, increased sebaceous secretion, and changes in facial, body, and scalp hair were uncommon, while voice changes have not occurred. In the two women with Cushing's syndrome, however, and in four patients receiving either prednisone or triamcinolone, methandienone did produce some androgenic effects, though these were never of a very severe degree, and did not necessitate the discontinuation of the drug. The increase in libido that occurred in some patients is of interest, and may indicate some androgenic action.

The relative lack of androgenic effect of methandienone in this series is particularly relevant in that initially we were uncertain of the dosage necessary to produce anabolism, and consequently in the early periods of our study we used an excessively high dose. From our present studies of nitrogen balance, doses of 0.2–0.4 mg./kg. body weight per day are capable of producing marked nitrogen retention and gain in weight. Initially many of the patients were given methandienone in doses in excess of 1 mg./kg. body weight per day.

In the rat, Desaulles *et al.* (1959) found that inhibition of oestrus could be brought about only by high doses of methandienone (30 mg./day)—methyltestosterone and norethandrolone being 30 times more active inhibitors of the oestrous cycle. They also found methandienone to have a very weak progestational effect, large doses (70 mg./kg.) being unable to produce a complete progestational type of secretory epithelium in castrated female rabbits sensitized with oestrone.

Foss (1960) found no suppression of the menses in two women given 25 mg. and 50 mg. of methandienone daily, though the drug caused suppression of the menses in one 14-year-old girl. In the small number of premenopausal patients in the present series who had normal and regular periods prior to starting methandienone, the drug has completely suppressed menstruation. The suppression of menstruation in these patients had persisted for from 100 to 200 days at the time of reporting this study. The suppression of menstruation and of menopausal symptoms is probably due to methandienone inhibiting the function of the pituitary gland.

Methandienone appeared to have no progestational effect. It caused no rise of body temperature, nor was there any withdrawal bleeding.

The increased sense of well-being found in many patients while on methandienone was of considerable therapeutic value. It did not occur in patients who were not symptomatically ill at the time of being given the drug, but was most pronounced in the older or chronically ill patient.

This sense of well-being may be attributable to the anabolic or possibly some other action of methandienone, rather than to any androgenic property. These changes were not similar to the euphoria seen in some patients on cortisone or in some patients with disseminated sclerosis or general paresis of the insane. It did not consist of unjustified cheerfulness, but occurred at a time of positive nitrogen balance, weight gain, and symptomatic improvement. It did not cause the undesirable psychological manifestations often seen with cortisone, such as nervousness, restlessness, and insomnia, nor did it ever produce a psychotic state.

Summary

During the past two years the effects of methandienone have been studied. Androgenic effects were slight or absent when a dose of the drug capable of producing marked anabolism was given, and, in several cases, even when the dose used was greater than that required to produce the maximum therapeutic effect.

Methandienone may suppress menstruation and menopausal symptoms when these are present.

In many patients, especially in the old or chronically ill, methandienone produced a sense of well-being and increased confidence. Unlike the effects of corticoid or corticotrophin administration, restlessness, nervousness, or insomnia did not occur.

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PREGNANCY IN AN ADRENAL PSEUDOHERMAPHRODITE TREATED WITH CORTISONE

BY

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Congenital adrenal virilism is caused by an inborn error of metabolism in which an inherited enzyme defect is responsible for excessive production of androgens and a diminished secretion of other cortical hormones (Jailer, 1953 ; Mason and Morris, 1953). The beneficial effects of cortisone, or its synthetic analogues, were demonstrated first by Wilkins *et al.* (1952): androgen production drops to normal and feminine characters emerge.

An obvious criterion of success in long-term therapy is the maintenance of a normal pregnancy. This paper records successful pregnancy and the birth of a normal child to a patient whose congenital adrenal virilism was not treated until adult life.

Case History

The patient, born in 1928, was seen at the London Hospital in 1954 complaining of amenorrhoea and beard-growth. At the age of 4 years enlargement of the clitoris had been noted and pubic hair was present at the age of 7. By the age of 11 she had a considerable amount of body hair, and facial hair growth had just begun. Subsequently this became so marked that daily shaving was required. Throughout childhood she grew faster than her contemporaries but stopped growing in her thirteenth year. From infancy until her fourteenth year she had suffered from episodic attacks of severe vomiting which prostrated her for two or three days. These attacks were usually precipitated by minor infections but became less severe and less frequent as she grew up. She had never menstruated.

Family History.—Four sisters were normal, but the fifth was suspected of having a genital abnormality. This girl (aged 8 years) was examined in 1954 and found to be an adrenal pseudohermaphrodite with virilism and a high 17-ketosteroid excretion. Treatment with cortisone diminished the virilism and in due course she went through a normal female puberty and achieved a regular menstrual cycle.

Examination (1954).—Female aged 25, height 4 ft. 10 in. (147 cm.). Limbs short in relation to height and very muscular. A diffuse brown pigmentation involved the skin and was accentuated over the fingers and present in the palmar creases. No buccal pigmentation was found. There was marked bitemporal recession of the scalp hair. The whole body was covered with coarse hair, the pubic hair spreading upwards to the umbilicus. The face was heavily bearded. There was no breast development. The genitalia were examined under anaesthesia. The clitoris was erectile and very hypertrophic. The urethra was separate from a normal vagina. The uterus was infertile, a sound passing only 1 in. (2.5 cm.). A salpingogram showed normal fallopian tubes. All other systems were normal. The blood-pressure was 120/70 mm.Hg.

Investigations.—Serum electrolytes were normal. Urinary 17-ketosteroids varied from 36 to 41 mg./24 hours. Total eosinophil count remained unchanged four hours after the intramuscular injection of 30 mg. of A.C.T.H.

Progress

The patient was treated with oral cortisone 25 mg. t.d.s. Her 17-ketosteroid excretion declined rapidly and then remained at between 6 and 12 mg./24 hours. After two months' treatment there was a definite growth of breast tissue and the skin pigmentation had faded. Menstruation occurred at that time, and from then onwards a regular menstrual cycle was established. Her scalp hair grew over the temporal areas but there was no significant change in the rate of beard growth.

After one year's treatment a further examination under anaesthesia was made. The uterus had enlarged and a sound passed 2 in. (5 cm.). Cortisone therapy at a total daily dose of 75 mg. was continued throughout, but as a result of the examination the 17-ketosteroid excretion rose temporarily from 15 to 31 mg./24 hours.

Subsequent progress on continued treatment was uneventful, but soon after marriage she conceived (last menstrual period June, 1959). She remained well throughout the pregnancy without any change in the dosage of cortisone. There was no hypertension, oedema, or albuminuria. In the 36th week a glucose-tolerance test was normal, the serum electrolytes were normal, but the excretion of 17-ketosteroids was 31 mg./24 hours. At the 38th week labour was induced by rupture of the membranes, but the head failed to descend properly owing to the small size of the pelvis, and the baby was delivered by caesarean section. The infant was a normal female, weighing 6¾ lb. (3,060 g.). Lactation began normally but had to be suppressed, as retracted nipples prevented the baby sucking.

Prior to the caesarean section 200 mg. of hydrocortisone was injected intramuscularly; otherwise, oral cortisone was continued at a dose of 75 mg. daily. Ten days after delivery the 17-ketosteroid excretion was 16 mg./24 hours. The puerperium was normal and the operation wound healed normally.

Discussion

Despite severe and prolonged virilization with primary amenorrhoea, the patient, at the age of 25, responded to cortisone therapy, which initiated a normal adult sex cycle that culminated in pregnancy. Fortunately she was born with a normal vagina and not the urogenital sinus commonly found in adrenal pseudohermaphrodites. The progressive virilization from childhood onwards was responsible for the android pelvic shape that prevented normal delivery. The association in her of a normal vagina and severe post-natal virilism illustrates the fact that the genital deformity at birth is related to the stage of embryogenesis at which abnormal adrenal function begins and is not correlated with the degree of adrenal androgen secretion in later life.

Gans and Ser (1959) reported a normal pregnancy in an adrenal pseudohermaphrodite treated with cortisone from the age of 16. Plastic repair of a urogenital sinus had been performed, but the baby was delivered by caesarean section because the lower genital tract was not regarded as suitable for normal delivery. Delivery by caesarean section was necessary for the patient recorded by Taylor (1958) because the android pelvis did not permit normal delivery. The diagnosis is somewhat dubious in the two cases reported by Wilson and Keating (1958) as the virilism appeared to be pubertal in onset, but their second patient required a caesarean section because of a contracted pelvis. The node of delivery in these cases depends on the size of the birth canal, and it is to be expected that the pelvis proportions will not be sufficient to allow normal delivery.

A rise in the 17-ketosteroid excretion as pregnancy progressed was found in the above case and in that of Gans and Ser. De Alvarez and Smith (1957), whose patient miscarried at the fourth month of pregnancy, had suggested that any rise of 17-ketosteroid excretion during pregnancy might be dangerous. However, these two pregnancies were normal throughout and the therapy remained unchanged. The rise in 17-ketosteroid excretion might be due to changes in intermediary metabolism or to increased pituitary activity despite continued cortisone therapy. A rise subsequent to the stress of anaesthesia was noted in the case reported here. The same mechanism may have been responsible for this and for the pregnancy change.

A history of vomiting attacks in childhood suggested that our patient suffered from recurrent minor episodes of Addisonian crisis. All patients with this type of adrenal disturbance are liable to adrenocortical insufficiency in response to stress. Consequently intramuscular hydrocortisone was given in addition to the regular dose of cortisone at the time of caesarean section. There was no evidence of adrenal insufficiency after operation, and it is suggested that such precautionary therapy is essential in all cases at the time of delivery, whether the birth is natural or by caesarean section.

The child born to our patient was a female with no genital deformity and with no evidence of adrenal insufficiency during her first weeks of life. The patients of Taylor and of Gans and Ser also gave birth to normal female infants. The children have not inherited their mothers' endocrine disorder, and their development was not affected by cortisone therapy.

Summary

A case of familial adrenal pseudohermaphroditism is described. Cortisone therapy initiated a normal menstrual cycle when the patient was 25 years old. Subsequent pregnancy was normal in all respects, but delivery had to be by caesarean section. A normal female child was born.

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SUCCESSFUL PREGNANCY IN A FEMALE PSEUDOHERMAPHRODITE

BY

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Although there have now been several reports of successful pregnancies in women with adrenal disease of different kinds, including Addison's disease, Cushing's syndrome, and adrenal hyperplasia of varying degrees of severity, such pregnancies in female pseudohermaphrodites requiring plastic genital operations (other than mere amputation of the clitoris) are still a rarity. The only report of such a case known to us is that of Gans and Ser (1959). A brief account of the case described below was given (Swyer, 1958) before the patient had conceived.

Case Report

A West Indian negro woman had come to England from Montserrat (Leeward Isles) two and a half years before she was referred to one of us (G.I.M.S.) in November, 1957, at the age of 24, complaining of primary amenorrhoea and abnormalities of the external genitalia. She wanted to get married and wished to know if she could be "made normal." She had five brothers and two sisters—the latter both married with children—all of whom were normal, and she knew of no relatives who had genital anomalies. Her past history was not remarkable.

Photograph of patient before treatment, showing male bodily configuration.

Her height was 5 ft. 0½ in. (136.6 cm.), weight 9 st. 5 lb. (59.4 kg.), and physical examination revealed a male bodily configuration (see Fig.) with wide shoulders, narrow hips, well-developed muscles, and undeveloped breasts. Facial hair was not present, but there were coarse skin pores. Axillary hair was copious and the pubic hair extended upwards over the lower abdomen to the umbilicus. The hair on the limbs was not excessive. The phallus was prominent, measuring 2.5 by 1.3 cm. (1 by ½ in.), and the urethra opened at its base. There were well-developed labio-scrotal folds, but no vaginal orifice could be seen. No inguinal gonads could be palpated. The patient was admitted for investigation.

Investigations. — Urinary 17-ketosteroids (17-KS) 123, 17-ketogenic steroids (17-KGS) 218, pregnanetriol (P'triol) 13.7 and 11.6, pregnanediol (P'diol) 3.5 and 3.1 mg./24 hours; oestrone 16.5, oestradiol 6.1, oestriol 10 μg./24 hours; gonadotrophins approximately 3 mouse uterine weight units/24 hours. Sex chromatin of urinary sediment smear and of neutrophils was positive. After prednisone, 5 mg. q.i.d. for four days, the 17-KS fell to 8.5, 17-KGS to 15.9, and P'triol to 0.2 mg./24 hours. *X*-ray examination after perirenal insufflation showed no evidence of adrenal tumour.

Laparotomy (Mr. D. N. Matthews).—A rather small uterus was seen, together with normal fallopian tubes and ovaries. The adrenals were palpated; the left was slightly enlarged, the right apparently normal in size.

Plastic Operation (Mr. D. N. Matthews).—Incision of the perineum revealed a sizable vaginal cavity which had no communication with the exterior. At the upper end the cervix was palpated. The vagina was dilated and a glass dilator was stitched in position, where it was left for 14 days. The clitoris was amputated, but the glans was retained.

Treatment and Progress

After recovery from the operations, adrenal suppressive therapy was begun on June 25, 1958, with prednisone 5 mg. t.i.d. At that time the 17-KS had risen to 33 mg./24 hours, but two months later they had fallen to 8.4 mg. The first period began 36 days after starting prednisone treatment, and breast changes had already been noticed by the patient. She had now married, and after a short time was able to have effective coitus. The 17-KS fell further to 4.8 mg./24 hours and the prednisone was reduced to 5 mg. b.d. By now she had had menstrual cycles of 34, 28, 32, 28, and 38 days. This last cycle was terminated by prolonged though scanty bleeding which continued for six weeks. The 17-KS rose to 38 mg./24 hours, and she complained of lower abdominal discomfort, dysuria, and malaise. A soft mass was palpable in the abdomen on the left. Pelvic inflammatory disease was suspected and she was admitted to hospital. Examination under anaesthesia (January 20, 1959) failed to reveal any unexpected abnormalities though curettage produced early decidua but no chorion. It was therefore concluded that she had probably had a tubal abortion.

Thereafter she had essentially regular cycles with basal temperatures showing a biphasic pattern, and the 17-KS remaining between 6.3 and 3.6 mg./24 hours, the prednisone dose having been kept constant at 5 mg. t.i.d. After a normal period on September 12, 1959, she had a scanty two-day loss from October 21. Her basal temperature record showed a post-ovulatory plateau continuing from October 1, and a pregnancy diagnosis test was positive on November 5. She was referred to the antenatal clinic but continued to have 17-KS determinations every two months. There was a slight rise, to a maximum of 15 mg./24 hours, at about the fourth month of gestation, but no change in prednisone dosage was found necessary.

The pregnancy progressed uneventfully and she was admitted on June 12, 1960, for elective lower-segment caesarean section. This was performed on June 17 with the delivery of a male baby, weighing 6 lb. 14 oz. (3,120 g.) and showing no congenital abnormalities. Lactation was established but the baby was a rather slow feeder; nevertheless its weight on discharge had risen to 7 lb. 2¼ oz. (3,255 g.). It has continued to thrive and at 20 weeks weighed 14 lb. 8 oz. (6,580 g.).

To cover the stress of delivery, intramuscular injections of prednisolone 20 mg. were given in the evening before operation, and again on the morning and evenings of operation. For the next three days prednisone 10 mg. t.i.d. orally was given, then 7.5 mg. t.i.d. for two days and thereafter 5 mg. t.i.d.

Menstruation was resumed on August 18, nine weeks after delivery, the next three cycles being of 18, 42, and 39 days.

Discussion

From clinical examination it was impossible to tell whether this patient was a male pseudohermaphrodite with abdominal testes, hypospadias, and a bifid empty scrotum or a female pseudohermaphrodite with congenital adrenal hyperplasia. The absence of marked

hirsutism seemed to argue against the latter, though from other points of view this seemed to be the most probable diagnosis. The findings on investigation soon settled the point: the very high 17-KS and 17-KGS and the elevated P'triol and P'diol pointed convincingly to adrenal hyperfunction, while the prompt response to prednisone suppression ruled against an adrenal tumour. The sex chromatin indicated female genetic sex, and laparotomy confirmed the existence of normal internal genitalia. Mr. Matthews found the construction of an effective vagina more straightforward than had been expected; incision of the perineum, dilatation, and the insertion of an indwelling dilator were all that was required and grafting was not necessary. It was an advantage that the patient married soon after, and fortunate that she was able to establish normal coitus with little difficulty.

The basis for the treatment of adrenal hyperplasia with suppressive corticosteroids, following the pioneer work of Lawson Wilkins and his colleagues, is now too well known to require discussion. It is, however, very striking that, even though the patient was 24 years old, her menarche occurred only 36 days after starting definitive prednisone therapy and fertility was established soon afterwards. This dramatic response in patients with severe congenital adrenal hyperplasia is uniformly seen and is, of course, extremely gratifying.

The smooth course of pregnancy, with only a minimal rise in 17-KS excretion, necessitating no change in prednisone dosage other than the prophylactic increase at the time of delivery, was perhaps rather unexpected though none the less pleasing. In the same way the good recovery from the caesarean section, the birth of a healthy baby, the establishment of lactation, and, more recently, the re-establishment of menstruation, have all been a source of great satisfaction.

Summary

A case of female pseudohermaphroditism due to congenital adrenal hyperplasia is described. This 24-year-old patient had primary amenorrhoea and no external vaginal orifice. The surgical construction of an introitus with dilatation of the vagina, and treatment with prednisone, led to the establishment of normal menstruation. She had what was concluded to have been a tubal abortion, followed, six months later, by a normal pregnancy. This proceeded uneventfully, and at 39½ weeks a male baby was delivered by elective caesarean section. Lactation was established, the baby thrives, and, more recently, menstruation has been re-established.

It is a pleasure to record our thanks to Mr. D. N. Matthews for carrying out the plastic surgery on this patient.

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During 1960, 10,427 deaths in London were reported to the coroner; 1,694 inquests and 8,733 inquiries without inquest were held into deaths; 536 cases of suicide were investigated, compared with 522 in 1959 and 557 in 1958. Of the 536 cases, 156 were of persons over 60 years of age. Four verdicts of murder were returned compared with 13 in 1959 and seven in 1958. Sixteen deaths were caused by chronic alcoholism compared with 23 in 1959 and 22 in 1958.

USE OF CORTICOSTEROIDS IN INFERTILITY ASSOCIATED WITH HIRSUTIES AND OLIGOMENORRHOEA

BY

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Congenital adrenal hyperplasia, caused by enzyme defects in the synthesis of cortisone, classically presents with prepubertal hirsuties, failure of breast development, and primary amenorrhoea. In this form at least, it is a rare disease. A much commoner clinical syndrome is that which presents after puberty with hirsuties, oligomenorrhoea, and infertility. It probably has a multiple aetiology (Ferriman, 1960). It may be due to a primary ovarian anomaly, to congenital adrenal hyperplasia of mild degree, or to a simple constitutional variant involving increased secretion of adrenal androgens. Certainly an adrenal factor appears to be concerned in an appreciable number of cases. Although 17-ketosteroid excretions may be normal, chromatographic separation shows that adrenal androgen secretion is frequently increased (Du Toit, 1951; Gardner, 1953; Johnsen, 1956; Perloff *et al.*, 1957; Gallagher *et al.*, 1958; Prunty *et al.*, 1958; Bush and Mahesh, 1959). Pregnanetriol excretion, another indicator of adrenal activity, is also raised above normal (Nabarro and Moxham, 1957; Gold and Frank, 1958; Prunty *et al.*, 1958).

It is now generally accepted that most of the disturbances in congenital adrenal hyperplasia may be corrected by the use of cortisone, and pregnancies have been reported (Wilkins *et al.*, 1955; Yamashita and Kozakae, 1956; de Alvarez and Smith, 1957; Wilson and Keating, 1958). It was reasonable, therefore, for its effect to be tried in the commoner clinical group of cases with which this paper is concerned, and a number of reports now indicate correction of both menstrual disturbance and infertility in a significant proportion (Jones *et al.*, 1953; Jones and Jones, 1954; Greenblatt *et al.*, 1956; Gold and Frank, 1958; Jefferies, *et al.*, 1958; Wilson and Keating, 1958; Jefferies and Levy, 1959).

This paper reports on a further group of patients with this condition.

Material and Methods

Altogether eight patients have been under study. Seven of these have fallen pregnant while under treatment with corticoids, and six have successfully borne children. One has failed to conceive.

A method of hair-scoring to be described by Gallwey and Ferriman (in preparation) has been used in six members of the group. The "hormonal" score has been found clinically useful, a score above 5 being regarded as unusual to the point of hirsuties. Marital

relations in all patients were stated to be satisfactory, and the frequency of coitus was adequate. Contraception was employed by some in the early days of marriage. The period of infertility, dating from cessation of this practice, is clearly more relevant than the date of marriage, and is therefore reported for each patient.

The optimal dosage of corticoids is unknown. Cortisone 25 mg. b.d. or prednisone 5 mg. b.d. is usually regarded as sufficient for suppression of adrenal function without producing undesirable side-effects, and these doses have usually been employed; any variation from this is stated. The common but not invariable absence of ovulatory cycles in these patients must be one factor responsible for their infertility. Other mechanisms may be involved, and it is possible that reduction of excessive androgen secretion may be necessary for the maintenance of pregnancy as well as its initiation; the frequency of abortion and miscarriage in these patients suggests such a possibility. It was decided, therefore, to continue corticoids for some months after conception. However, three patients aborted while taking corticoids, and in their subsequent successful pregnancies corticoids were discontinued three weeks after conception. Cortisone was discontinued three weeks after conception in a fourth patient on two occasions; the first pregnancy terminated in abortion three weeks later, but the second went on to termination for toxaemia at the 38th week.

Cases in which Conception Took Place During Corticoid Therapy

Case 1.—The patient was first seen at the age of 28, complaining of infertility. She was always large, and became somewhat obese from the age of 25. Menarche at 11. At first the menstrual cycle lasted four weeks, but this lengthened to five to six weeks from the age of 20. A basal temperature chart kept for one year showed cycles to be ovulatory. Height, 69 in. (175 cm.); weight, 15st. 10 lb. (99.8 kg.). Hormonal hair score, 8. Urinary excretion of 17-ketosteroids, 24.3 mg./24 hours. Prednisone 5 mg. b.d. was started on May 12, 1959, the patient then having been infertile 18 months. The basal temperature chart indicated conception on May 21. Prednisone was continued. Figures for the 24-hour urinary excretion of 17-ketosteroids had fallen to 9.6 mg. in June, but rose again to 20.3 mg. in July and September, and to 42.5 mg. in December. This apparent rise in 17-ketosteroid excretion was presumably due to interference from pregnanolone, excretion of which is increased during the later stages of pregnancy (Martin and Mills, 1958). The December figure, however, appears unusually high. Abortion threatened in the third month and again in the fourth month, and was treated by rest in bed, with continuance of the pregnancy. Prednisone was discontinued in the 34th week. Labour started spontaneously in the 35th week and she was delivered of a healthy male child weighing 5 lb. 5 oz. (2,410 g.).

Case 2.—This patient was first seen at the age of 29 in May, 1953, complaining of obesity, oligomenorrhoea, and hirsuties. Menarche at 16. Menstrual cycle, 5–16 weeks. A basal temperature chart kept for the next three years showed three out of four cycles to be ovulatory. Height, 62 in. (157.5 cm.); weight, 10 st. 8 lb. (67.1 kg.). Hormonal hair score, 15. Urinary 17-ketosteroid excretion, 19.1 mg./24 hours. Cortisone 25 mg. b.d. was started in October, 1956, the patient then having been infertile 18 months. Conception took place a few days later. Cortisone was continued and she aborted one month later. Cortisone was resumed in December. Four ovulatory cycles were followed by conception in May, 1957. Cortisone was stopped three weeks later. A full-term healthy male child was born in February, 1958.

Case 3.—First seen in December, 1956, at the age of 27, complaining of infertility. Menarche at 12. The menstrual cycle was of about 30 days' duration. Basal temperature charts showed only three out of the next six cycles to be ovulatory. Height, 64 in. (162.5 cm.); weight, 12 st. (76.2 kg.). Hormonal hair score, 11. Urinary 17-ketosteroid excretion, 28.4 mg./24 hours. Cortisone 25 mg. b.d. was started in August, 1957, the patient then having been infertile three and a half years. Three ovulatory cycles were followed by conception in October, 1957. Cortisone was continued and she aborted two months later. Cortisone was discontinued, one out of the next three cycles being anovulatory. Cortisone was resumed in April, 1958. Six ovulatory cycles then occurred, and were followed by conception in October, 1958. Cortisone was stopped three weeks later. A full-term healthy female child was born in June, 1959.

Case 4.—This patient was first seen in 1957 at the age of 39, complaining of infertility. Menarche at 15. Menstrual cycle, 28–31 days. A basal temperature chart showed six ovulatory cycles. Height, 61 in. (155 cm.); weight, 12 st. (76.2 kg.). Hormonal hair score, 13. Urinary 17-ketosteroid excretion, 16.7 mg./24 hours. Cortisone 25 mg. b.d. was started in April, 1958, the patient then having been infertile three and a half years, apart from one pregnancy at one year terminating in abortion after three months. She conceived in November, 1958. Cortisone was discontinued three weeks later. She aborted three weeks later after a strenuous day's shopping. Cortisone was resumed in January, 1959. She conceived after one ovulatory period. Cortisone was again stopped after three weeks, and abortion threatened three weeks later. She was treated by rest in bed and sedation. She stayed in hospital for two months, mostly in bed, as bleeding recurred on getting up. She left hospital eventually when four months pregnant. Mild signs of toxaemia appeared later in pregnancy. A healthy female child was delivered by caesarean section at term.

Case 5.—The patient was first seen in November, 1956, at the age of 25, complaining of hirsuties and oligomenorrhoea. Menarche at 16. The menstrual cycle varied from six weeks to six months. Height, 63 in. (160 cm.); weight, 8 st. 7 lb. (54 kg.). A basal temperature chart kept for seven months showed six cycles, of which five were ovulatory. No obesity. Hirsuties, present from her teens, involved the lip, chin, breasts, lower abdomen, and thighs. Prednisone 5 mg. b.d. was started in June, 1958, the patient then having been infertile for approximately four years, apart from a pregnancy at three years terminating in abortion at three months. Two ovulatory periods, in July and August, were followed by conception in October. Prednisone was discontinued after six months. The patient was delivered of a full-term healthy male child in June, 1959.

Case 6.—The patient was first seen in September, 1957, at the age of 24, complaining of obesity and hirsuties. Marked obesity had developed from the age of 20. Menarche at 17. Menstrual cycle, five to six weeks. Height, 62 in. (157.5 cm.); weight, 13 st. 6 lb. (85.3 kg.). Hirsuties of two to three years' duration affected the face, breasts, sacral area, lower abdomen, and thighs. Prednisone 5 mg. b.d. was started in March, 1958, the patient then having been infertile approximately five years. This was increased to 5 mg. t.d.s. in December, and shortly after that she conceived. She discontinued tablets of her own volition one month later, and abortion occurred in April, 1958. She has failed to keep further appointments.

Case 7.—This patient was first seen in June, 1954, at the age of 29, complaining of oligomenorrhoea. Menarche at 13. Menstrual cycle, one to two months. Basal temperature charts kept for the next three years showed mostly anovulatory cycles. Height, 63 in. (160 cm.); weight, 15 st. (95.3 kg.). The hormonal hair score was only 3. However, a frankly hirsute sister with oligomenorrhoea and a hormonal hair score of 9 was seen later. The patient's urinary 17-ketosteroid excretion was 15.6 mg./24 hours. It is believed,

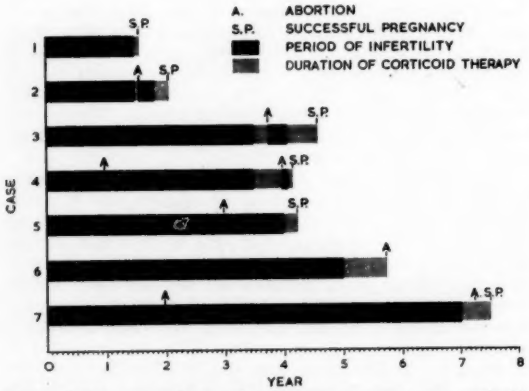
therefore, that this patient belongs to the group under discussion. A wedge resection of the ovaries was carried out in 1955. The ovaries were normal in size, but contained a number of small follicular cysts. Ovulatory activity was not improved. Cortisone 25 mg. b.d. was started in July, 1957, the patient then having been infertile seven years, apart from one pregnancy at 2 years, terminating in miscarriage after 4–5 months. She conceived in October, 1957, after two doubtfully ovulatory periods. Cortisone was continued, and she aborted six weeks later. She continued to take cortisone and, after two menstrual cycles with short progestational phases, conceived in February, 1958. Cortisone was stopped three weeks from conception. Mild toxaemia developed later in pregnancy, and labour was induced at the 38th week. A healthy male child weighing 6 lb. 8 oz. (2,950 g.) was born in October, 1958.

Cases in which Conception Did Not Take Place During Corticoid Therapy

Case 8.—The patient was first seen in 1954 at the age of 20, complaining of abdominal pain; she was found to be pregnant. Menarche at 16. Menstrual cycles were regular at monthly intervals until the age of 18, when they lengthened to between two and nine months. Height, 62 in. (157.5 cm.); weight, 9 st. (57.2 kg.). Hormonal hair score, 8. Urinary 17-ketosteroid excretion, 12.2 mg./24 hours. One healthy male child had been born out of wedlock in 1954. She married the child's father in 1955 and practised contraception until 1957. She then discontinued this practice and expressed a wish for a child. Cortisone 25 mg. b.d. was started. She discontinued the tablets of her own volition six months later. There had been no improvement in menstrual behaviour nor had pregnancy ensued. She has been followed for a further two and a half years and conception has not taken place. Salpingography has shown patent fallopian tubes.

Discussion

Important features of those cases in which pregnancy occurred during corticoid therapy are illustrated in the Chart. It must be pointed out that in two cases the periods of infertility prior to treatment were rather short



Data relating to patients who became pregnant on corticoid therapy.

—18 months. However, it is suggestive that seven out of eight patients became pregnant within a few days to nine months from starting corticoids, after periods of infertility ranging from 18 months to 7 years. The time relationships involved are particularly suggestive, and this is brought out in the Chart, where periods of infertility are contrasted with duration of corticoid therapy prior to conception. Taken in conjunction with the experience of others reported above, the evidence presented here is thought to justify further trial of corticoid therapy in this group of cases.

A tendency to abortion seems to be a feature of the syndrome, both spontaneously and after the use of corticoids. It was of common occurrence prior to operation, for example, in the large series of cases treated with wedge resection of the ovaries by Stein (1955). It has been common in the reported series treated with corticoids, and occurred during treatment in no fewer than five of our patients. The question arises whether corticoids should be continued throughout pregnancy. Neither our own nor other series provide any clear answer to this. What seems fairly clear is that threatened abortion needs prompt treatment along traditional lines with rest and sedation.

Summary

The effect of corticosteroids is reported in eight patients suffering from hirsuties, oligomenorrhoea, and infertility. Seven fell pregnant and six successfully bore children. A comparison between the duration of therapy prior to contraception and the preceding periods of infertility suggests that corticosteroids were responsible for the relief of infertility in at least some of the patients. A tendency to abortion was common. Three patients had experienced abortions prior to treatment, and five aborted during treatment. The literature is reviewed. It is concluded that corticosteroids may have a part to play in the treatment of these patients.

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Social Workers, a new booklet in the "Choice of Careers" series, issued by the Central Youth Employment Executive, is concerned with professional social workers and gives many details of the wide range of opportunities for those who feel that they would find interest and satisfaction in a career spent in helping others. (H.M.S.O., price 1s. 3d.)

DIETHYLPROPION IN THE TREATMENT OF "REFRACTORY" OBESITY

BY

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Diethylpropion ("tenuate") is a recently introduced anorectic agent which reduces the food intake of experimental animals without causing undesirable stimulation of the central nervous system (Martin, 1959). Its efficacy as an adjuvant to the dietary treatment of obese persons is, however, unproved, as the few clinical observations reported were uncontrolled and inadequate (Ravetz, 1959; Spielman, 1959; Wilson and Long, 1960). We report the results of a controlled double-blind trial of diethylpropion in obese persons who had failed to respond to dietetic instruction during the previous year and whose obesity we have defined as being "refractory" (Duncan *et al.*, 1960).

Methods

Selection of Patients

All the 48 patients selected were women. Each patient (1) had reported regularly to the dietetic department throughout the previous year for supervision of the treatment of her obesity with a suitable diet of 1,000 to 1,400 calories; (2) had lost little or no weight during this time or in the three months before starting the trial; (3) was visibly obese and overweight by at least 25% of her standard weight; and (4) was not known to have heart disease and had no detectable oedema. Two patients in each group had very mild diabetes but showed minimal glycosuria and were not taking insulin or a sulphonylurea.

These patients were divided into two deliberately matched groups (Table I). Four in each group had to be withdrawn during the trial—two failed to report, one left the district, and one became ill with cholecystitis—and four were admitted to hospital on account of carcinoma, varicose ulceration, myocardial infarction, or increasing incapacity due to obesity. The last patient, who was in group B, weighed 350 lb. (158.8 kg.) at the beginning of the study and had been matched with the patient of group A who weighed 337 lb. (152.9 kg.); the retention of the latter accounts for the difference in the standard deviations in the mean absolute weights of the two groups. These patients who were withdrawn did not differ in terms of their change in weight during the study from the others receiving the same tablets. The essential facts about the 40 patients who completed the trial are set out in Table I. Many of them had taken part in a previous trial of phenmetrazine ("preludin") and methylcellulose (Duncan *et al.*, 1960), but no patient had taken any anorectic drugs during the previous year.

TABLE I.—*Data Concerning the Two Groups of Patients*

	Group A		Group B	
No. of patients	20		20	
Age (years) ..	56·3 (43–71)		54·4 (34–67)	
*Body weight:	lb.	kg.	lb.	kg.
1 year before trial	195·4±40·2 (157–340)	88·6±18·23 (71·2–154·2)	195·8±25·7 (162–257)	88·8±11·66 (73·5–116·6)
3 months before trial	195·9±38·2 (165–336)	88·9±17·37 (74·8–152·4)	195·2±22·2 (161–255)	88·5±10·07 (73·0–115·7)
Change in 3 months preceding trial	+3·9±3·6 (−2–+11)	+1·77±1·63 (−0·91–+4·99)	+2·1±2·9 (−1–+10)	0·95±1·32 (−0·45–+4·54)
At start of trial	199·8±37·7 (169–337)	90·6±17·10 (76·6–152·9)	197·3±23·1 (163–265)	89·5±10·43 (73·9–120·2)
†"Standard weight"	140·5±8·4 (126–164)	63·7±3·81 (57·2–74·4)	138·9±7·3 (129–151)	63·0±3·31 (58·5–68·5)
Excess weight at start of trial	59·4±32·3 (35–173)	26·9±14·65 (15·9–78·5)	58·4±22·5 (34–126)	26·5±10·21 (15·4–57·2)
Excess weight at start of trial as % of standard weight	41·9±19·6 (25–106)		41·7±15·6 (26–90)	

* Values are means, standard deviations, and ranges.
† Standard weight for each patient was derived from tables of the U.S.A. Medico-Actuarial Investigation, New York, 1912.

Initial Procedure

One month before starting the trial all the patients were seen both collectively and individually, and the purpose of the study was explained. They were told, (1) that they would receive two types of tablets whose identity would be unknown to them and to those concerned with the study; (2) that these tablets might or might not help them to eat less and thus to lose weight; (3) that they were to continue to try to adhere to the dietary regime which they were supposed to have been following during the previous year; (4) that they would not be told their weight and were not to weigh themselves; (5) that they should wear, as nearly as possible, the same indoor clothes at each visit. At this visit each patient was weighed and then allocated to one group. Thereafter each reported to a special clinic at fortnightly intervals.

Tablets Administered

The diethylpropion tablets each contained 25 mg. of the drug and did not differ in appearance, texture, or taste from the dummy tablets; the latter contained 0.25 g. of mannitol, 70 mg. of starch, and a small quantity of magnesium stearate. They were supplied by the manufacturers in bottles containing 56 tablets and labelled "O" or "X"; this identification was removed and the tablets were dispensed in bottles bearing only the patient's name. The nature of the tablets was made known to us only after completion of the trial and analysis of the results. The patients took four tablets daily, one half an hour before each of the three main meals and one in the late evening.

Further Conduct of Trial

Each patient reported fortnightly for 24 weeks. She was weighed in indoor clothing on a regularly standardized lever-type balance and her weight was made known to A. M. S. only. The patient was then seen by D. A. S., L. J. P. D., or K. R.; any subjective effects spontaneously attributed to the tablets were noted, but direct inquiry regarding specific effects was avoided. The patient was then given a bottle containing 56 tablets. A datum sheet was kept for each patient. These were held by A. M. S., who recorded on them the patients' weights and comments; none of these data was divulged to the medical or dietetic staff until completion of the study.

Results

Changes in Weight.—Table II shows that the administration of diethylpropion for 12 weeks resulted in a fall in the mean weight of both groups of patients and

that the taking of dummy tablets resulted in an increase. It can be seen from Table III, however, that the reduction in mean weight occurred only in the first eight or so weeks of the diethylpropion treatment and that an increase followed thereafter. This is illustrated in the Chart. Nevertheless, the progressive rise in the mean weight of the patients when receiving dummy tablets was sufficient to make the difference between their responses to the two preparations statistically highly significant at all times ($P<0.001$). The impression that diethylpropion loses its efficacy in most patients after six to eight weeks of its daily administration is supported by the data set out in Table IV.

Subjective Effects.—The change from one type of tablet to the other was not noticed by any patient.

TABLE II.—*Influence of Administration of the Two Preparations on Body-weight of the Two Groups of Patients*

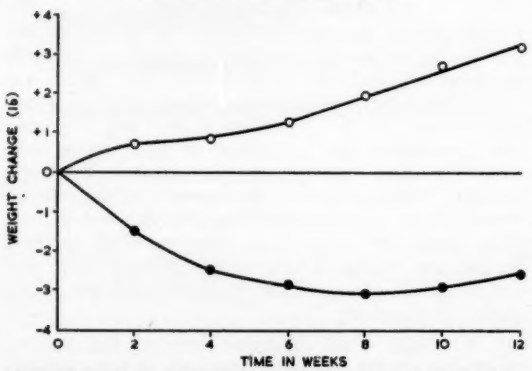
Period			Group A	Group B
	Initial weight*	lb.	199·8±37·7 (169–337)	197·3±23·1 (163–265)
		kg.	90·6±17·10 (76·6–152·9)	89·5±10·48 (73·9–120·2)
	After 12 weeks administration of:		Diethylpropion tablets	Dummy tablets
1	Weight	lb.	198·5±37·8 (165–336)	199·7±26·7 (159–268)
		kg.	90·0±17·14 (74·8–152·4)	90·6±12·11 (72·1–121·6)
	Change in weight	lb.	−1·33±5·07 (−10–+8)	+2·33±4·82 (−10–+11)
		kg.	−0·60±2·30 (−4·54–+3·63)	+1·06±2·19 (−4·54–+4·99)
	After 12 weeks administration of:		Dummy tablets	Diethylpropion tablets
2	Weight	lb.	202·3±38·5 (168–339)	195·9±27·3 (153–258)
		kg.	91·8±17·46 (76·2–153·8)	88·9±12·38 (69·4–117)
	Change in weight	lb.	+3·78±3·95 (−5–+9)	−3·78±4·34 (−10–+9)
		kg.	+1·71±1·79 (−2·27–+4·08)	−1·71±1·97 (−4·54–+4·08)

* Values are means, standard deviations, and ranges.

TABLE III.—*Mean Cumulative Weight Change of Groups A and B Combined during their Treatment With the Two Preparations*

Duration of Treatment (Weeks)	Weight Change			
	Dummy Tablets		Diethylpropion	
	lb.	g.	lb.	g.
2	+0·67 (±1·9)	+304 (±862)	−1·47 (±2·3)	−667 (±1,043)
4	+0·75 (±2·2)	+340 (±998)	−2·58 (±3·7)	−1,170 (±1,678)
6	+1·19 (±2·8)	+540 (±1,270)	−2·81 (±3·8)	−1,275 (±1,724)
8	+1·94 (±3·3)	+880 (±1,497)	−3·11 (±4·1)	−1,411 (±1,860)
10	+2·75 (±4·2)	+1,247 (±1,905)	−2·89 (±4·2)	−1,311 (±1,905)
12	+3·06 (±4·4)	+1,388 (±1,996)	−2·56 (±4·9)	−1,161 (±2,223)

Values are means and standard deviations.



Mean cumulative weight change of both groups combined when receiving the dummy tablets (○—○) and diethylpropion (●—●).

Indeed, many thought that the two types of tablets were being alternated every fortnight and others thought that each bottle contained both types of tablets; one of the latter remarked that every second tablet had a bitter taste. Table V lists the effects attributed by patients to the tablets. Of the 10 patients who felt less hungry when taking diethylpropion, eight were losing, one gaining, and one was not changing in weight.

TABLE IV.—*Pattern of Weight Change of the 40 Patients when Receiving the Two Preparations*

Type of Change in Weight	Diethylpropion	Dummy Tablets
Steady increase throughout the 12 weeks	5	19
,, ,, for 4 to 8 weeks and no change thereafter	0	8
No change during the 12 weeks	3	6
Steady loss throughout the 12 weeks	7	3
,, ,, for 4 to 8 weeks and no change thereafter	11	4
Steady loss for 6 to 10 weeks and gain thereafter	14	0

TABLE V.—*Subjective Effects Reported During Administration of the Two Preparations*

Side-effect Reported	Diethylpropion	Dummy Tablets
Increased appetite	0	5
Decreased ,,	10	2
Dry mouth	8	0
Difficulty in sleeping	2	2
More excitable	1	0
Depressed	1	0
More energy	3	2
Less ,,	4	1
Nausea	1	1
No changes	18	30

Discussion

Patients who for the first time seek medical treatment for their obesity usually adhere to the prescribed diet for some months and lose weight during this time; many continue to lose weight and achieve the desired standard. Although anorectic drugs may well accelerate initial loss of weight their use is neither required nor justified for these patients; they are therefore unsuitable subjects for the clinical evaluation of such agents. Nevertheless, many obese persons fail after a time to control their appetite, cease to lose weight, and may indeed put it on again. We have, as in a previous study (Duncan *et al.*, 1960), deliberately selected such patients for the clinical trial of diethylpropion as they are the only persons for whom an anorectic agent might be advantageous.

When subjected to this practical test diethylpropion caused a mean loss of weight which was significantly different from the mean gain in weight which occurred when the same patients were taking dummy tablets. The anorectic properties of the drug were therefore demonstrated, and it is possible to assess its mean efficacy in this respect. The caloric value of 1 g. of adipose tissue is 6 calories (Keys and Brožek, 1953), and the difference in mean weight of the 40 patients after 12 weeks of treatment with each preparation was 5.6 lb. (2,540 g.) (Table II). From these data we calculate that the caloric value of the daily diet eaten by the patients when taking diethylpropion was about 190 calories less than when they were receiving the dummy tablets. This represents about 2¼ oz. (66 g.) of bread, ½ pint (280 ml.) of milk, or ¾ oz. (21 g.) of butter.

Nevertheless, the absolute loss of weight caused by the diethylpropion was very small; 20% of the patients did not lose weight and 80% of those who lost weight did so only during the first 6 to 10 weeks of treatment

and thereafter remained at that weight or gained weight. This latter type of response agrees with the generally accepted view that anorectic agents lose their efficacy in most patients within a relatively short time and that their long-term administration is valueless (Adlersberg and Mayer, 1949).

Diethylpropion did not cause any serious side-effects. In particular there was no evidence of undue central nervous stimulation or insomnia; a few patients noticed dryness of the mouth.

Consideration of the results of this study together with those of similarly conducted trials of the amphetamines and phenmetrazine (Edwards and Swyer, 1950; Duncan *et al.*, 1960; Hampson *et al.*, 1960), shows that there is little difference between the weight-reducing influence of the three drugs. Although the amphetamines and phenmetrazine are apt to cause central nervous system stimulation and may lead to addiction, it is justifiable to compare the costs of the drugs. The cost to the National Health Service of one month's treatment with each preparation when the tablets are prescribed in quantities of 100 on form E.C.10 and dispensed in Scotland is as follows:

	s.	d.
Diethylpropion (tenuate) tabs. 25 mg. q.i.d.	28	7
Phenmetrazine (preludin) tabs. 25 mg. t.i.d. ..	16	5
"Benzedrine" tabs. 5 mg. t.i.d.	5	10
"Dexedrine" tabs. 5 mg. t.i.d.	5	1
Tab. amphetamine sulphate *B.P.* or *B.N.F.* 5 mg. t.i.d.	3	6
Tab. dexamphetamine sulphate *B.P.* or *B.N.F.* 5 mg. t.i.d.	2	7

Finally, it is appropriate to consider the response to strict dieting of the very obese patient in group B, who was withdrawn from the trial because of increasing depression and physical incapacity due to her vast size. When admitted to hospital she weighed 355 lb. (161 kg.), and had no physical evidence of excessive fluid retention. For 10 weeks she was given a 600-calorie diet; during the first four to six weeks her activities were limited, but thereafter her daily caloric expenditure was increased by about 600 calories by walking. Over these 10 weeks a steady weight loss of 34 lb. (15.4 kg.) occurred, which is almost exactly that expected from the calculated mean daily deficit of 1,300 calories. During this time she did not experience hunger and was satisfied with her diet. This response is frequently seen in such patients dieted in hospital; it emphasizes that gross and persistent overeating is often due to psychological disturbances or habit, and therefore may well be refractory to the influence of the most effective of anorectic agents. It also refutes any suggestion that the obesity was due to irreversible abnormalities of appetite or metabolism and could not, therefore, be corrected by suitable reduction of food intake.

Summary and Conclusions

A double-blind trial of diethylpropion tenuate was carried out on 40 obese out-patients who had proved refractory to dietetic advice alone.

The difference between their mean gain in weight when given dummy tablets and their mean loss of weight when taking diethylpropion was statistically highly significant at all times during the 12 weeks' administration of each preparation. The absolute weight loss was, however, disappointingly small and similar to that previously recorded with the amphetamines and phenmetrazine (preludin). No important side-effects occurred.

Like other anorectic agents, diethylpropion lost much of its effect in most patients after 6 to 10 weeks of treatment. Apart from its expense, diethylpropion seems to be a suitable drug for use as a short-term adjunct to the dietary treatment of obesity.

We are grateful to Professor Sir Derrick Dunlop for his helpful advice and to Dr. D. Mansel-Jones, of Merrell-National (Laboratories) Ltd., who supplied the preparations used. Our thanks are also due to Miss E. Wilson and Miss M. Kellock for their invaluable help in the dietetic aspects of the trial.

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Medical Memoranda

A Case of Genital Prolapse in a Newborn Baby

Genital prolapse in the newborn is a rare condition usually associated with spina bifida. The following record is of a baby who showed no evidence of an associated lesion and who has made an apparently complete recovery after replacement of the prolapsed uterus. Some features of the mother's pregnancy and labour suggested that her abnormal uterine action was the important aetiological factor.

Case Report

A married woman aged 23 was referred to the antenatal clinic at 35 weeks with a breech presentation. One year previously she had an abortion at 11 weeks, but her medical history contained no significant feature.

During her present pregnancy there had been very slight vaginal bleeding at 5 and 13 weeks. A breech presentation, corrected at 34 weeks by external cephalic version, had recurred.

On her first visit to the clinic a midline fundal "dimpling" was noted and a provisional diagnosis of a degree of uterine duplication was made. Attempted version was again unsuccessful. At 37 weeks the impression of a fundal depression was confirmed, but exact palpation was difficult and the breadth of the uterus aroused a suspicion of twins. A flat abdominal film showed a single foetus presenting by the breech with both legs extended. Erect lateral pelvimetry demonstrated a true conjugate of 4.35 in. (11 cm.) and a pubo-sacral diameter of 4.25 in. (10.8 cm.). The pelvic shape appeared normal.

On later examinations the uterus felt normal and the foetal parts were much more readily palpable. The baby seemed small, and it was decided to await the spontaneous onset of labour in anticipation of a normal vaginal delivery, with the proviso that caesarean section be performed should progress not be satisfactory.

The patient was admitted to hospital three days before term. The membranes had ruptured spontaneously and clear liquor was draining. No contractions had been felt, the breech was free, and the foetal heart was satisfactory. Vaginal examination excluded cord prolapse.

After some hours mild contractions began, and continued throughout the day, but did not cause discomfort severe enough to require analgesics. Twenty hours after membrane rupture, morphine sulphate, ¼ gr. (16 mg.) was given in an attempt to ensure a good night's rest in anticipation of improved uterine action the next day, but the palpable contractions remained weak and irregular. The breech had not entered the pelvic brim.

Thirty hours after rupture of the membranes the foetal heart rate rose to 160 a minute. Initially the rhythm was regular, but within 10 minutes there was irregularity followed by rapid variations in rate between 120 and 160 a minute. The contour of the uterus was normal and there was no impression of hypertonic uterine action. The cervix was dilated two finger-breadths and no cord prolapse was palpable. In view of the foetal distress and uterine inertia probably on the basis of minor pelvic contraction, caesarean section was performed.

Operation

A lower-segment caesarean section was carried out under thiopentone, nitrous oxide, cyclopropane, and ether anaesthesia with relaxants. The uterus appeared to be normal and there was no drawing up or oedema of the bladder, which was reflected easily from the lower uterine segment. There was a notable lack of bleeding on incision of the uterus. The legs were flexed and delivered easily, followed by the trunk and arms. Difficulty was suddenly experienced in attempting to deliver the head, and on palpation of the interior of the uterus a tight constriction-ring was felt about the child's neck. The anaesthetic was deepened and an attempt made to stretch the ring digitally and apply Wrigley's forceps. This was unsuccessful, but jaw and shoulder traction, combined with fundal pressure by an assistant, effected the delivery of an asphyxiated girl of 5 lb. 15½ oz. (2,705 g.) who responded to resuscitation.

The Infant

After delivery the ring was still palpable to a lesser degree about the middle of the uterus. The placenta was removed manually after the injection of ergometrine, 0.5 mg., into the uterine muscle, and careful exploration of the cavity did not show any evidence of a septum. The uterine exterior and adnexa were normal. Despite the deepening of the anaesthesia the avascularity of the uterine incision was maintained and the operation was completed without any further complication. The puerperium was normal.

A congested oedematous mass protruded from the baby's vulva. The apex of the mass was the cervix, and the whole uterus appeared to lie outside the introitus. A transverse ridge corresponding to the bladder was visible. The mass appeared to become more congested and oedematous before the examiner's eyes, and, as the baby was still pale and shocked, digital reposition was performed. This was done easily, with an immediate improvement in the baby's condition.

The baby was observed closely on crying and there was no recurrence of the uterine prolapse nor occurrence of rectal prolapse. Digital examination at the end of a week showed the cervix to be well supported at a high level. The introitus admitted an average-sized index finger more readily than expected.

Follow-up examinations of the infant were performed 3 and 17 months after delivery and no abnormality was found. There had been no sign of recurrence and bowel and bladder function was normal. She had walked at 11 months, and the lumbar spine, sacrum, and external genitalia were normal to inspection and palpation. Radiological examination showed no evidence of spina bifida.

DISCUSSION

Findley (1917) stated that genital prolapse in the newborn was usually not detected at birth but after the first week; and in his series it was associated with spina bifida in 86% of cases.

Noyes (1927) reviewed 24 bona-fide cases from the literature (not all of these were in the newborn) and concluded that spina bifida was the primary aetiological factor. The lower sacral nerve roots, particularly the fourth sacral, are drawn through the lumbar vertebral defect to produce a partial or complete paralysis of the pelvic floor musculature.

Radwansky (1898) recorded a case in which the prolapse was detected on the day after delivery and replaced successfully, with a satisfactory result on examination six months later. Spina bifida occulta was not excluded in this instance.

Malpas (1955) has classified the causes of prolapse into: (*a*) primary—for example, congenital tissue-weakness, obstetric trauma; and (*b*) secondary—for example, raised intra-abdominal pressure. Had congenital tissue-weakness been an important factor in the above case one would have expected a recurrence, with the stresses of crying and defaecation. It is possible that raised intra-abdominal pressure due to abnormal uterine action was the primary cause.

Palmer (1951) described a series of apparent abnormalities of the uterus which were observed at caesarean section and were due to abnormal uterine action. A similar mechanism may have produced the impression of a bicornuate uterus noted at the antenatal clinic. During labour there was no clinical evidence of hypertonic uterine action—rather the reverse. The avascularity of the lower segment was remarkable, and, with the contraction ring, did seem to indicate hypertonus. The alterations in the foetal heart rate and rhythm could be explained by embarrassment of the utero-placental circulation, by pressure on the cord, or by alteration of the circulation within the foetus.

My thanks are due to Mr. P. R. Mitchell, under whose care the patient was admitted, for permission to publish this report.

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Peripheral Neuropathy in Association with Carcinoma of Thyroid

Neurological syndromes associated with cancer, not due to metastatic deposits, were first noted by Oppenheim (1888), and occasional cases were recorded by Nonne (1900), Siefert (1902), Parkes Weber and Hill (1933), and Greenfield (1934). However, it was not until the report by Denny-Brown (1948) of sensory neuropathy in two patients with carcinoma of the lung, in which he demonstrated degeneration of the posterior root ganglia at necropsy, that the association became widely accepted. A variety of syndromes are now recognized (Brain and

Henson, 1958). They occur most often with carcinoma of the lung, but also in association with cancer of many other organs. However, neurological complications accompanying carcinoma of the thyroid have not yet been described.

Among the neurological syndromes, peripheral neuropathy has been recorded only in association with carcinoma of the bronchus, and on one occasion with carcinoma of the oesophagus (Dodgson and Hoffman, 1953). A case is now reported of carcinoma of the thyroid associated with peripheral neuropathy.

CASE HISTORY

A 55-year-old Jewish housewife was first seen on October 14, 1958, complaining of numbness and paraesthesiae of both legs of three weeks' duration. At this time no neurological abnormalities were detected, but a small lump was noted in the thyroid gland. Investigations showed an iron-deficiency anaemia (haemoglobin 68%, P.C.V. 35%, M.C.H.C. 25%), and treatment with ferrous gluconate was started. One week later she complained of weakness of the right foot, and examination showed impaired dorsiflexion. As this weakness progressed the patient was admitted on November 17 for further investigation.

On admission right foot-drop and weakness of the dorsiflexors of the left foot were found. Both ankle-jerks were absent. All types of sensation were impaired over both feet, and plantar responses could not be elicited on either side. The nodule previously noted in the thyroid was a small, smooth, hard lump situated in the suprasternal notch, apparently in the isthmus of the gland. It was not attached to the skin or other structures. There was no other abnormality on physical examination.

Investigations.—Haemoglobin, 68%; total white cell count, 27,200/c.mm. (polymorphs 61%, lymphocytes 36%, monocytes 1%, eosinophils 2%); reticulocytes, 2%; blood W.R. and Kahn, negative. Lumbar puncture normal; cerebrospinal fluid normal. Fasting blood sugar and glucose-tolerance test normal; serum alkaline phosphatase, 8 K.-A. units; fractional test meal, normal. *X*-ray films of the chest and cervical spine and a barium swallow were normal. The raised white-cell count fell to normal within four weeks and was unexplained.

During the first few days in hospital the neuropathy progressed until the patient had complete bilateral foot-drop with almost total sensory loss over the feet. Treatment with oral iron was continued and she was given intramuscular thiamine, 100 mg. daily. The haemoglobin did not rise, nor did the neuropathy improve, although no further progression occurred. Electromyograms of the right and left anterior tibial muscles on December 16 showed marked fibrillation with only a few motor units present on volition. The findings were thought to be evidence of a severe neuropathy.

Meanwhile, although the nodule in the thyroid did not alter, the hardness suggested a carcinoma, and it was decided to remove it. At operation it appeared to be a completely encapsulated tumour in the isthmus of the gland and was easily enucleated. Histological examination showed a well-differentiated papillary adenocarcinoma infiltrating the capsule at several points. In view of this report it was decided that the patient should have a total thyroidectomy. This was performed on April 11, 1959. Examination of the fragments removed showed no histological evidence of carcinoma.

Within two weeks of the first operation the neuropathy had started to improve. Recovery was steady and eight months later there was minimal weakness of dorsiflexion of both feet; the ankle-jerks were still absent, but sensation was normal, and both plantar responses were easily elicited and flexor. Electromyography on May 19 showed that some fibrillation was still present, but there were many normal units and some polyphasic units on volition. It was concluded that a considerable degree of recovery had occurred. The patient remained anaemic because she refused to take iron preparations.

COMMENT

There are many causes of peripheral neuropathy, among which occult carcinoma is not common. When the above patient was first seen the lump in the thyroid was not regarded as carcinomatous and a search for a commoner cause for the neuropathy was pursued. Her diet was adequate, and she had not taken any drugs before the onset of her illness, nor had she been exposed to any toxic substance known to cause peripheral neuropathy. There was no history of trauma or of preceding acute infection. A normal fasting blood sugar and glucose-tolerance test excluded diabetes mellitus. The patient had an iron-deficiency anaemia with a normoblastic marrow. Nothing suggested vitamin-B_{12} or folic-acid deficiency. The negative W. R. and Kahn test excluded a syphilitic neuropathy. There was no clinical evidence of peripheral vascular disease and no family history of neurological disease. A normal chest *x*-ray picture was thought to exclude a bronchial carcinoma as the cause of the neuropathy. Although a pyruvate-tolerance test was not performed, the failure of the neuropathy to improve after six weeks' treatment with parenteral vitamin B was thought to exclude a deficiency of this factor.

The neuropathy did not appear to be due to any of the common causes, and, although the initial rapid progression of the lesion ceased, no improvement was apparent after six weeks in hospital. However, within two weeks of removal of what proved to be an adenocarcinoma of the thyroid, objective evidence of recovery was present and was followed by steady improvement. Whether this was related to the removal of the carcinoma or was entirely fortuitous is impossible to prove. Brain and Henson (1958) consider that regression of neurological syndromes after excision of an associated cancer is coincidental, and many observers have reported spontaneous remission of peripheral neuropathy in association with untreated carcinoma of the lung. The mere fact that recovery from the neuropathy followed removal of a malignant tumour cannot, therefore, be taken as evidence for a causal relationship between the two. Nevertheless, the association of the neuropathy with carcinoma of the thyroid in this case is thought to be worth recording, if only to emphasize the need to search for malignant disease in all patients with unexplained peripheral neuropathy.

I thank Dr. L. H. Worth, under whose care the patient was admitted, for his help and encouragement, and wish to acknowledge the help of Mr. C. I. Murphie, who performed both operations, Dr. J. A. U. Morgan, who reported on the histology, and Dr. G. O. Storey, who carried out the electromyograms.

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Reviews

THE ETHICAL DILEMMA

The Ethical Dilemma of Science and Other Writings. By A. V. Hill. (Pp. 395+xiii. 52s.) New York: Rockefeller Institute Press. London: Oxford University Press. 1960.

The subject of Professor Hill's memorable presidential address to the British Association in 1952 gives the title to this volume. Science being universal, his ideal—an ideal shared by all true scientists—would be a world-wide community of learning, irrespective of politics, in which "world society can see a model of international co-operation carried on not merely for idealistic reasons but because it is the obvious and necessary basis of any system that is to work."

In this imperfect world the free, open, and disinterested pursuit of knowledge, divorced from political influences, seems impracticable. There are, for instance, the compromises enforced by the demands of secrecy and officialdom, when scientific researches are used for national security; and ethical considerations which perplex the scientist. There is no simple answer to the problem, but the author, out of his wisdom and experience, gives some helpful suggestions. His conclusion (p. 88) is as follows:

> "It is true that scientific research has opened up the possibility of unprecedented good, or unlimited harm, for mankind, but the use that is made of it depends in the end on the moral judgments of the whole community of men. It is totally impossible now to reverse the process of discovery: it will certainly go on. To help to guide its use aright is not a scientific dilemma but the honourable and compelling duty of a good citizen."

The problem of the increase of world population, especially in India, resulting from the triumphs of preventive medicine, is also discussed.

Notes, all too short, about some great physiologists are here—Einthoven, Pavlov, Starling, Bayliss, for instance. Those who knew Joseph Barcroft, so enthusiastic and devoted in his study of blood and respiration, will welcome this sketch of a great and generous man. Tributes are given to the work of Sir Henry Dale, Lord Adrian, and others; there is a sensible note on germ warfare; and the Stephen Paget Lecture to the Research Defence Society treats of the benefits to mankind accruing from animal experiments.

Like Michael Finsbury in *The Wrong Box*, Professor Hill indulges in "a little judicious levity." He inserts parodies, verses, and satire as light relief in a mainly serious book. Anyone who has unexpectedly, temporarily, and possibly for no fault of his own become famous in the popular press will appreciate the amusing chapter on "The Donnan–Hill Effect [The Mystery of Life]," written by Mrs. Hill and her sister-in-law, Margaret Keynes.

ARTHUR S. MACNALTY.

VASO-ACTIVE POLYPEPTIDES

Polypeptides Which Affect Smooth Muscles and Blood Vessels. Proceedings of a Symposium held in London on March 23 and 24, 1959. Edited by M. Schachter, M.D., M.Sc. (Pp. 336+xv; illustrated. 50s.) Oxford, London, New York, Paris: Symposium Publications Division, Pergamon Press. 1960.

One of the most striking recent advances in pharmacology has been the recognition of the existence of a variety of vaso-active polypeptides, circulating in or produced in the blood-stream. Interest in these fascinating substances has been greatly stimulated by the elucidation of the structure and the subsequent synthesis of oxytocin, vasopressin, and angiotensin.

This report presents the full report of the fifth symposium organized by the Biological Council's Co-ordinating Committee for Symposia on Drug Action, others having been concerned with hypotensive drugs, 5-hydroxytryptamine, and quantitative methods in human pharmacology and therapeutics.

Where pure substances of known structure are available, our knowledge of their pharmacological action, in animals and in man, and of the various processes of inactivation is increasing rapidly. The demonstration of naturally occurring analogues, in different animals, as well as the synthesis of active analogues, has added much to our understanding of peptide structure and action. The presence of many of these substances, however, such as Substance P, leucotaxine, and the kinins, can still only be demonstrated by their pharmacological effects, though it should not be long before their structure too is known.

The section on angiotensin (hypertensin) illustrates the many difficulties of work with these compounds. The existence of a humoral hypertensive agent having been demonstrated in animals with ischaemic kidneys, angiotensin was ultimately isolated, identified, synthesized, and its pharmacological action defined, and yet there is still no clear evidence that it is responsible for renal hypertension in man.

The organizing committee are to be congratulated on having brought together so many of the original workers in this complex field, and this report not only provides an excellent review of present knowledge but gains much from the reported discussions.

M. L. ROSENHEIM.

INVALIDISM AND REHABILITATION

Invalidität und Rehabilitation in ärztlicher Sicht. Edited by Dr. med. A. Wernli-Hässig. (Pp. 183; illustrated. Sw. Fr. 30.) Basel and New York: S. Karger. 1961.

This book contains the proceedings of a postgraduate course on invalidism and rehabilitation convened by the "Zürich Kantonalen Liga gegen die Tuberkulose" in March, 1960. In an introductory paper, the editor, Wernli-Hässig, surveys the achievements in the prevention and treatment of tuberculosis in Switzerland during the last 10 years or so. There has been a decrease in morbidity from 3.8 to 2.1 per 1,000 and in mortality from 3.9 to 1.5 per 10,000 inhabitants. To-day, tuberculosis, properly treated, leads to death only in exceptional cases. The empty tuberculosis sanatoria in Switzerland are, as is the case in other countries, now used for the treatment of other diseases, such as asthma, chronic bronchitis, and circulatory and neuro-vegetative disturbances.

All the other twelve lectures of the course deal with the medical and social rehabilitation of patients suffering from non-tuberculous afflictions, such as congenital, traumatic, vascular, and mental diseases. Of special value are the papers of Francillon and Mützel on orthopaedic problems, Brügger and Krayenbühl on rehabilitation following head injuries and brain operations, Mohr on rehabilitation and psychiatry, and Hegglin on rehabilitation in vascular diseases.

Only in recent years have new national insurance laws been introduced in Switzerland, which include measures for the education, training, and industrial resettlement of severely physically handicapped people; measures which, in due course, will facilitate the re-integration into society of those with severe disabilities, such as spinal paraplegia. In recent years, leading neurosurgeons and orthopaedic surgeons in Switzerland, such as Krayenbühl and his colleagues Weber and Brügger, as well as Francillon and Müller, have drawn the attention of the public to the lack of satisfactory facilities in Switzerland for the treatment and rehabilitation of those handicapped by disorders of the spinal cord. As a result doctors and nurses have been sent to Stoke Mandeville for training in this complex aspect of medicine, and now, as Francillon and Mützel point out in their lectures, some progress is being made in the rehabilitation of these patients.

LUDWIG GUTTMANN.

TEXTBOOK OF OPHTHALMOLOGY

Augenheilkunde. Ein Lehrbuch für Studium und Praxis. By F. Rintelen. (Pp. 455+xxvii; illustrated. Sw.fr. 65.) Basle, New York: S. Karger. 1960.

This is a new textbook of ophthalmology designed for the medical student by a well-known Swiss professor of the specialty. It covers the entire subject topographically, each tissue of the eye, its adnexa, and the associated central nervous mechanisms being discussed under such headings as anatomy, congenital deformities, injuries, inflammations, circulatory disturbances, degenerations, tumours, and so on. There are some interesting appendices—statistics of the causes of blindness as seen in the author's clinic at Basel (uveitis 15.4%, myopia 11.6%, and simple glaucoma 11.5% have the highest incidence), a short history of the development of ophthalmology, the derivation of the more common medical terms in which ophthalmology abounds, a short pharmacopoeia, and a short biographical note of some of the great personages who have served the specialty. The book is interestingly and simply written without being burdened with excessive detail, the teaching is sound and classical, and the unusual excellence and abundance of the illustrations are explained by the fact that they were underwritten by pharmaceutical firms. For those who read German it offers a very acceptable and simple exposition of its subject.

STEWART DUKE-ELDER.

ERYTHROPOIETIC FACTORS

Factors Controlling Erythropoiesis. By James W. Linman, M.D., and Frank H. Bethell, M.D. (Pp. 208+ix; 66s.) Springfield, Illinois: Charles C. Thomas Company, Ltd. 1960.

An increasing amount of work on the importance of humoral factors in the normal and pathological control of erythropoiesis is appearing in the journals. This book provides a timely review of what has been published so far, and, since the authors have themselves worked on this problem, they have been able to make a valuable critical assessment of this work. The subject is still very much in the development stage and there are quite a lot of discrepancies and disagreements to be settled, but Linman and Bethell think that there is enough agreement for a useful progress report.

The problem has been the subject of intermittent research since 1906, when Carnot and Delandre showed that the serum of rabbits that had been bled when injected into normal rabbits could cause a rise in red-cell counts. Research has now excluded the known endocrine glands from any such primary control; the anaemia of myxoedema and the polycythaemia of Cushing's syndrome are secondary reflections of the metabolic effects of these endocrine diseases. Attention has been concentrated on the plasma factors; more than one has been described; and the authors list five approaches to the problem that have been used. These are the development of methods of detecting activity; the gathering of information about the physical, chemical, and physiological properties of the factors; the detection of sites of production; the measurement of activity in abnormal conditions in patients with anaemia, polycythaemia, and hypoxia, and in animals with similar experimentally induced conditions; and finally attempts to measure the erythropoietic potency in extracts or concentrates of plasma. The account of these approaches forms the subject-matter of this book, and it is notably complete and up to date. At the end of each chapter a paragraph beginning "In summary" gives a clear indication of the present situation and the authors' views.

A full bibliography of 370 references is provided, text figures are clear, and the style not too afflicted by research jargon. The book is essential for anyone considering work in this field, and will surprise others by the amount of work already carried out. There is still much to be done before any practical application of the information about humoral erythropoietic factors can be thought about, but this book makes out a very good case for continuing research.

M. C. G. ISRAËLS.

ENZYMES IN DIAGNOSIS AND TREATMENT

Enzymes in Clinical Medicine. By Irving Innerfield, M.D. (Pp. 334+ix; illustrated. 89s.) New York, Toronto, London: Blakiston Division, McGraw-Hill Book Company, Inc. 1960.

A British clinician asked to define medical enzymology is likely to consider only the diagnostic use of enzymes; there has as yet been little enthusiasm in this country for possible therapeutic applications. The present work, however, gives greater prominence to the latter aspect, and for this reason will not be universally acceptable. As befits the originator of buccal enzyme therapy, two-thirds of the book are devoted to a closely reasoned and persuasive account of the value of proteolytic enzymes in the treatment of a wide variety of inflammatory, oedematous, and thrombotic conditions. Substances such as chymotrypsin and streptokinase are believed to function as activators of naturally occurring plasminogen, which in the presence of tissue injury is converted to plasmin. The latter increases tissue permeability and lyses fibrin, and is thus responsible for liquefaction of inflammatory exudates and intravascular thromboses. These proteolytic enzymes can be given parenterally or as aerosols, but are also effective by mouth because they activate salivary plasminogen. Certainly the results claimed by the author are impressive.

A short chapter follows on the well-known carbonic anhydrase and monoamine oxidase inhibitors, and the rest of the book is concerned with diagnostic enzymes. Here we are on more familiar ground, and this section can be recommended as giving a lucid summary, not

easily obtainable elsewhere, of the value of phosphatases, transaminases, peptidases, lactic dehydrogenase, and many other enzymes in diagnosis. It is perhaps strange that, in a work which claims to be comprehensive, there is no mention of glucose oxidase. The book is meant for the clinician, and so a simple introduction to enzyme theory would have been helpful, as well as a more critical evaluation of some of the extensive literature to which the valuable bibliography bears witness.

A. PATON.

GYNAECOLOGICAL ANATOMY

Atlas der Gynäkologischen Anatomie. By Heinrich Martius and Käthe Droysen. (Pp. 118+viii; illustrated. DM. 49.) Stuttgart: Georg Thieme Verlag. 1960.

This slim volume is really an adjunct to the authors' well-known textbook on gynaecological operations. It was apparently produced separately to keep the larger volume within reasonable proportions, but even so it more than justifies independent publication. The illustrations, which naturally provide the main interest, are accurate in detail and beautifully drawn by Käthe Droysen, and the text, in three languages, is clear and succinct. A disadvantage, however, is the separation of the two parts, the description occupying the first half of the book and the drawings the second. This entails for the reader a good deal of looking back (in spite of the short accompanying captions), and might well be modified in future editions. A further disadvantage inherent in the atlas is its compression into little more than 100 octavo pages, each further diminished by language reduplication. To encompass the whole field of the developmental, microscopical, and gross anatomy of the female genitalia in this space is obviously impossible, and the result is a book too elementary for the specialist while too complicated for the student. It is, however, an admirable attempt to cover a long-neglected sector of gynaecological teaching, and both tyro and expert will derive much pleasure and profit from the study of this beautifully produced volume.

ALBERT DAVIS.

ELECTRICAL ACTIVITY OF NERVOUS SYSTEM

The Electrical Activity of the Nervous System. A Textbook for Students. By Mary A. B. Brazier, B.Sc., Ph.D.(London). (Pp. 273+xiv; illustrated. 35s.) London: Pitman Medical Publishing Co., Ltd. 1960.

Dr. Brazier writes with authority and experience, and the reader is stimulated throughout this monograph by the synthesis of the two approaches on the two sides of the Atlantic (not to mention the Pacific too). The three "new" techniques developed largely since the last war —namely, electronic amplifying methods, the electro-encephalogram, and micro-electrodes—have indicated new phenomena and produced new interpretations. All this is apart from the biochemical and molecular aspects being developed in "non-electrical" areas of the subject —if a biological phenomenon exists which is non-electrical.

The rediscovery that the all-or-none law applies to conducting fibres only and not to receptors, effectors, or neurons has reopened closed minds. Graded responses can be re-analysed; the neuron is now accepted as an electron-microscopical object whose parts have each different functions and activities. The integrative action of the central nervous system has been extended beyond the limits of Sherrington in that the C.N.S. controls receptors by modulating their messages and by producing greater fusion between sensory and motor systems. Further, the analysis of the reticular formation bridges the gaps between experimental physiology, behaviourism, and psychology.

The author "looks forward to a book being written in 1969 on the electrical activity of the nervous system." Meanwhile this text is clear and logical, and will help the educated student or doctor wanting to be brought up to date in this field, whether registrar, general practitioner, consultant, or teacher.

A. ST. G. HUGGETT.

CONFLICT IN MARRIAGE

Marriage: Studies in Emotional Conflict and Growth. Edited by Lily Pincus, with Eight Contributors. Introduction by A. G. Thompson, M.D., F.R.C.P.I. (Pp. 259+vii. 25s.) London: Methuen and Co., Ltd. 1960.

This book is compiled by a number of "case workers" on the staff of the Family Discussion Bureau. This bureau is a special kind of Marriage Guidance Council, it would seem. All its members are psychoanalytically trained and work on psychoanalytical lines; and the Bureau has elaborated a technique of its own for dealing with marital problems. Each marital partner has regular interviews with his (or her) own case-worker (i.e., the same worker does not deal with the problems of both husband and wife); and it is rare for the four people concerned to be confronted with each other at a common interview. The theory behind practice is that marriages go wrong because one or both (usually both) of the partners are psycho-sexually immature; in other words, their lives are unconsciously determined by undesirable identifications with or fixations on their own parents. Practice consists of interpretations of that kind being put to the patient whenever the transference situation justifies it. The insight obtained by the acceptance of such interpretations would appear to have a very good therapeutic effect; and many marriages which would otherwise have broken up seem to have been saved.

It is undoubtedly true that many unions fail on account of the existence of sexual neurosis in one or both partners; and it is good to learn that situations of this kind can be met without full-scale, long-drawn-out analysis. However, it seems to me that the majority of unsuccessful marriages are due to moral factors: selfishness, unwillingness to make sacrifices, lack of tenderness, self-indulgence, and the like. These factors would not, I think, easily lend themselves to correction by the psychoanalytical method.

E. B. STRAUSS.*

SOME ASPECTS OF FLUORIDATION

Medical and Dental Aspects of Fluoridation. By W. A. Cannell, M.R.C.S., L.R.C.P., D.P.H., L.D.S. R.C.S. (Pp. 125 +vii. 15s.) London: H. K. Lewis and Co. Ltd. 1960.

This book is obviously the product of much reading. Its title might lead one to expect a careful discussion of the use of fluorides in the prevention of dental disease and the dangers to the teeth and other tissues arising from the use of these materials. Perhaps this is an unreasonable expectation, for of ten chapters six contain little mention of fluorides and their effects. Nowhere in this book is there any critical assessment of the effects of fluorides on the incidence of dental caries, nor is there any review of present knowledge on the causation of caries. There are, however, four chapters dealing

*Dr. Strauss died on January 11.

with the calcification and structure of dental tissues. In these as in many other chapters the author writes with an authority too frequently unsupported by facts or references.

There is a remarkable number of mistakes, possibly printer's errors, though they occur with some consistency, for example, the use of the word "calorimetric" for "colorimetric" and "hydroxapatite" for "hydroxyapatite." References are at times misquoted or misspelt, and the style of English is sometimes so tortuous as to mislead not only the reader but the author.

In the introduction the author states that the book is intended for clinicians and research workers, but it is unlikely that either will find it of great value.

A. I. DARLING.

NEUROLOGY OF INFANCY

Neurology of Infancy. By Anatole Dekaban, M.D., Ph.D. (Pp. 388+xiv; illustrated. 96s.) London: Baillière, Tindall and Cox, Ltd. 1959.

The author has written this book with two main objects—to give information about the maturation of the central nervous system during the first two years of life, and to describe the various neurological disorders that occur in infancy. His first chapter deals with developmental anatomy and physiology, the second with clinical examination, and the subsequent fifteen chapters with pathological conditions. A wide field has been covered, and it is to be hoped that in subsequent editions the author will try to achieve a better balance by some rearrangement and by pruning out the unnecessary—e.g., chorea—and amplifying the more important—e.g., epilepsy. A number of repetitions could be usefully cut out, and more cross-references would be helpful. There are also many spelling mistakes to be corrected.

This work will be useful to neurologists who have not had much experience of infants, but I feel that paediatricians—in Great Britain, at all events—will be disappointed not to find more detailed information than is available to them at present in the larger textbooks of children's diseases. They would welcome an up-to-date account of neurological advances that specially concern them in their care of young children, but clearly it would need to be selective. Dr. Dekaban's book contains nearly 200 excellent plates and illustrations, which add considerably to the reader's interest and give point to the text. Fig. 66 shows right facial palsy, not left, as stated in the caption.

Each chapter concludes with a valuable list of bibliographical references.

N. B. CAPON.

Proceedings of Conferences

Among the proceedings of conferences which have recently been published are the *Proceedings of the Pneumoconiosis Conference held at the University of Witwatersrand, Johannesburg, February 9–24, 1959* (J. and A. Churchill Ltd., 1960; 632 + xvi pp.; illustrated; index; price £6). The conference was sponsored by the South African Council for Scientific and Industrial Research. The Institut de Médecine Tropicale Prince Léopold, Anvers, has published an account of its *Premier Colloque International sur les Mycobactéries* held on December 4, 5, and 6, 1959. (1960; 198 pp.; illustrated; no price given.) The *Proceedings of the Third International Congress on Medical Records* has been published by E. and S. Livingstone. The Congress was held in the Assembly Rooms, Edinburgh, from April 25 to 29, 1959. (350 pp.; 45s.)

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Kanker en Hormonen. By Dr. J. Samuels. Third edition. (Pp. 96. Fl. 4.90.) Hoorn, Netherlands: Uitgevers-Maatschappij 'West-Friesland.' 1961.

Der Eidophor. Eine Schweizerische Entwicklung der Fernseh-Grossprojektion. By Ernst Baumann. (Pp. 51; illustrated. No price.) Zurich: Kommissionsverlag Gebr. Fretz AG. 1961.

The Veterinary Annual. Editor: W. A. Pool, M.R.C.V.S. Second issue. (Pp. 384+xxiv; illustrated. 38s. 6d.) Bristol: John Wright and Sons Ltd. 1960.

The Story of X-Rays from Röntgen to Isotopes. By Alan Ralph Bleich, B.A., M.D. (Pp. 186+xiv; illustrated. 11s.) New York: Dover Publications, Inc. London: Constable and Company Ltd. 1961.

The Glycolysis and Respiration of Tumors. By Alan C. Aisenberg. (Pp. 221+xiii. $8.) New York and London: Academic Press. 1961.

Evaluation of Drug Therapy. Proceedings of the Symposium on Evaluation of Drug Therapy in Neurologic and Sensory Diseases held at the University of Wisconsin, May, 1960. Edited by Francis M. Forster. (Pp. 167+xxiv. $4.) Madison: The University of Wisconsin Press. 1961.

Miscellaneous Notes. (Tenth Series.) By F. Parkes Weber, M.D., F.R.C.P., F.S.A. (Pp. 7. 2s. 6d.) London: H. K. Lewis and Co. Ltd. 1961.

Biological Clocks. Cold Spring Harbor Symposia on Quantitative Biology. Volume XXV. (Pp. 524+xiii; illustrated. $12.) New York: The Biological Laboratory, Cold Spring Harbor, Long Island, New York. 1960.

Slice Reconstructions of Human Cerebral Sections. By Wendell J. S. Krieg, Ph.D. (Pp. 25. No price.) Evanston, Illinois: Brain Books. 1960.

The Year Book of the Royal Society of London 1961. (Pp. 302. £1 1s.) London: The Royal Society, Burlington House, Piccadilly, W.1. 1961.

Klinik und Therapie der Pilzkrankheiten. Revised by Dr. G. Polemann, Dr. T. Wegmann, Dr. A. Stammler. Edited by Priv.-Doz. Dr. G. Polemann. (Pp. 396+xi; illustrated. DM. 67.) Stuttgart: Georg Thieme Verlag. 1961.

Back to Berlin. An Exile Returns. By V. B. Carleton. (Pp. 309. 18s.) London: Sidgwick and Jackson. 1961.

Experiences in Groups and Other Papers. By W. R. Bion. (Pp. 198. 20s.) London: Tavistock Publications. 1961.

Moral Principles of Fertility Control. By Denis O'Callaghan, D.D. (Pp. 39. 2s. 6d.) Dublin: Clonmore and Reynolds Ltd. London: Burns Oates Ltd. 1960.

Artificial Feeding in Early Infancy. By Andrew Bogdan, M.D., M.R.C.P.E., D.C.H. (Pp. 24. 3s. 6d.) Leeds: Austick's Medical Bookshop, 53 Great George Street. 1961.

Meaning and Methods of Diagnosis in Clinical Psychiatry. By Thomas A. Loftus, M.D. (Pp. 169. 37s. 6d.) London: Henry Kimpton. 1960.

Cell Physiology of Neoplasia. A Collection of Papers Presented at the Fourteenth Annual Symposium on Fundamental Cancer Research, 1960. (Pp. 653; illustrated. $10.50.) University of Texas Press. 1960.

Electron Microscopy in Anatomy. Proceedings of a Symposium held by the Anatomical Society of Great Britain on the Ultra-structure of Cells. (Pp. 288+viii; illustrated. 50s.) London: Edward Arnold (Publishers) Ltd. 1961.

Mathematical Biophysics. Physico-Mathematical Foundations of Biology. By N. Rashevsky. Third revised edition. Volume 1. (Pp. 488+xxvi+15. $2.50.) New York: Dover Publications, Inc. 1960.

Mathematical Biophysics. Physico-Mathematical Foundations of Biology. By N. Rashevsky. Third revised edition. Volume 2. (Pp. 462+xi+15. $2.50.) New York: Dover Publications, Inc. 1960.

Visual Field Defects after Penetrating Missile Wounds of the Brain. By Hans-Lukes Teuber, William S. Battersby, Morris B. Bender. (Pp. 143+xi; illustrated. 38s.) London: Oxford University Press. 1960.

Carcinogenesis. By I. Hieger. (Pp. 138+xi. 35s.) London and New York: Academic Press. 1961.

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ACCIDENT NEUROSIS

Since more than a million people are injured yearly at work or on the roads, it is surprising that the literature on accident neurosis is so scanty, the more so in view of the large sums of money paid out in compensation to the many victims of accidents. The main features of accident neurosis have been known for some time: that it more commonly follows trivial injuries, or even none at all, than severe ones; that it has a class incidence; and that it rarely follows injuries on the sports field, where the question of compensation does not arise. These would seem to confirm that the condition is not the result of the accident but is related to the desire for compensation and the hope of financial gain. This is the conclusion of Dr. Henry Miller, whose two Milroy lectures, delivered before the Royal College of Physicians in February, appear in this and last week's issues of the *Journal*.

Dr. Miller describes a series of 200 consecutive cases of head injury (152 male and 48 female) first referred for medico-legal examination between 1955 and 1957. Excluding those cases with post-concussional symptoms, depressive syndrome, and organic impairment, he was left with 47 with undoubtedly neurotic symptoms who formed the main subject of study. The average age of these patients was 42, and it was found that accident neurosis was twice as common after industrial as after road accidents and more than twice as common in men as in women. No matter how the cases were analysed, they showed conclusively an inverse relationship between accident neurosis and the severity of the injury. "Gross psychoneurosis occurred, for example, in 31% of patients without radiological evidence of skull fracture, in 9% of patients with simple fracture, and in only 2 out of 25 patients who suffered compound fractures of the skull." An inverse relationship also existed between the appearance of gross symptoms and the period of unconsciousness after the accident. In respect of social status and the nature of employment, it was found that only 18% of the patients held responsible posts above the level of charge-hand; more came from the large industries, whether nationalized or privately owned, than from the small family business; and there was a higher-than-average proportion of cases from dangerous jobs such as steel-erectors and underground mine-workers, where claims for compensation are an everyday matter. Not unnaturally both the patients and their relatives were firm in the conviction that rude health had existed before the injury, but on the whole this was confirmed by the family doctor; for, though bad work records sometimes entailing long absences were common after trivial injuries, more than half the patients showed no predisposition to neurosis. So far as absence from work was concerned, Dr. Miller's figures show that all but the most severe head injuries cause less disablement than accident neurosis.

What can the family doctor do to help in this situation? By the time that litigation is impending, he is unfortunately likely to have become the least significant figure of the trio, litigant, lawyer, and physician, and he is likely to be visited solely with a view to obtaining medical certificates. All attempts at therapy by this stage are doomed to failure and may even arouse paranoid suspicions in the patient, who has every intention of entering the witness-box with his full complement of symptoms. Behind the exaggeration and dramatization, the "terrible" headaches, and the rest, the patient betrays his total lack of interest in the whole question of treatment, though he will passively submit to prolonged physiotherapy. This, indeed, is usually his lot, and closer co-operation between the orthopaedic surgeon and the psychiatrist might be appropriate. Dr. Miller is clear that few of his cases could by any stretch of imagination be described as iatrogenic, but it seems likely that many could be nipped in the bud if early on the patient was weaned away from his impending neurosis by a physician who had the courage of his convictions. The worst thing the doctor can do in such cases is passively to accept the patient's exaggerations: it is best to make it clear in the early stages that complications are not expected. The really litigious patient will not thereby be prevented from pressing his claim, but many who are hovering on the brink may be prevented from entering a situation which is not in their own interest in the long run. Above all, both the general physician and the orthopaedic surgeon would find it advisable to refer a patient to the psychiatrist as soon as possible when this state appears to be developing, for it is clear that a definite statement that his symptoms are or are not attributable to the effects of physical injury plays a major part in the patient's recovery. At the very least such a step would save much futile physio-

therapy and long stays in convalescent homes, where the patient, so far from being helped, is merely confirmed in his suspicions and educated to develop more. The fact that in a series of 50 cases followed up by Dr. Miller only two were still disabled by their psychiatric symptoms two years after settlement shows that elaborate treatment is not only useless but unnecessary. Accident neurosis, as he convincingly points out, is closely related to an attitude of mind which still retains the old "us" and "them" polarity within the confines of a Welfare State. In the ultimate analysis it is a social disease and a function of industrial morale.

MORTALITY FROM CHLORAMPHENICOL

When it became generally recognized in 1952 that chloramphenicol can cause marrow aplasia, there was a steep fall in the quantity of this antibiotic used. Since then the quantity prescribed has again increased considerably. This toxic effect, some research into which was recently discussed in these columns,[1] is evidently no longer regarded generally as a contraindication, at least to a course of limited length and dosage. An important influence in producing the change of attitude was the conclusion, obtained from surveys of the frequency and apparent causation of aplastic anaemia, that this is so rare a complication as to be an almost negligible risk. If indeed only 1 patient in 100,000 given the drug developed this complication, such an attitude might be justified, but there are indications that the incidence is not so low. Several of the authors of the original papers on this subject saw not single cases but several. During the intervening years other such reports have appeared: M. Lamy and his colleagues[2] saw three fatal cases in children in two years in Paris, and R. G. Shaw and J. A. McLean[3] described seven cases, six of them fatal, "encountered in Melbourne in the last 12 months." These authors believe that the true incidence of this complication has not been ascertained; they also question the possibility of defining a safe system of dosage, since some of their patients had had only short courses, the total dose in two of them being 3.5 and 8 g. So far as England and Wales is concerned, a notable item of information was recently published by the Registrar-General.[4,5] During 1956–8 there were 856 deaths from aplastic anaemia or agranulocytosis, of which 83 were attributed to drugs or other therapy. Chloramphenicol was incriminated in 19 of these, and over 50 other drugs in most of the remainder, each contributing very few cases.

A further warning which it would surely be rash to ignore now comes from no less an authority than W. Dameshek, of Boston.[6] He begins by saying that within one recent month he saw four new patients with aplastic anaemia to all of whom chloramphenicol had been given for minor respiratory infections. In a series of 30 such cases seen in three years eight had been treated with chloramphenicol, including five of the most recent ten cases. He continued: "The tragic thing about all these seriously ill cases, most of whom died, is *that the drug need never have been given*" (his italics). It was noteworthy in the original 1952 reports that the indications for the fatal treatment were often woefully inadequate. Dameshek has four remedies to suggest, the first being education of the medical profession itself. Patients and their relatives also need to be warned that this is a powerful drug, that it should be used only once and not "kept in the bathroom cabinet and used again if an apparently similar disorder supervenes." "Detail men" (travellers) should be instructed "not to minimize the dangers of the drug, and to emphasize its value for certain specific conditions, and not for the whole gamut of infectious diseases." Finally, "By some means, whether by regulation or by self-discipline, promiscuous use of the drug should be avoided and its use restricted to *impelling circumstances*, i.e., for conditions in which no other antibiotic is currently effective."

It is unfortunate that the distinguished author could not go further and define what in his view these conditions are, for this is the essence of the whole matter. C. Wilson[7] has said that the only indications for chloramphenicol are typhoid fever and *H. influenzae* meningitis. Septicaemia and meningitis due to other chloramphenicol-sensitive Gram-negative bacilli would equally be so, but these are rarities. What of the treatment of whooping-cough: is this justified? In what circumstances may chloramphenicol be given for chronic bronchial infections? Long-term administration is generally admitted to be unsafe, and the innocuous though (for this purpose) rather less effective tetracyclines have to be substituted, but can an acute exacerbation justifiably be treated? Or should the drug be used

[1] *Brit. med. J.*, 1961, **1**, 650.
[2] Lamy, M., Jammet, M.-L., Frézal, J., Lasfargues, G., and Lortholary, P., *Bull. Acad. Med. (Paris)*, 1958, **142**, 565.
[3] Shaw, R. G., and McLean, J. A., *Med. J. Aust.*, 1957, **1**, 352.
[4] *Registrar-General's Statistical Review of England and Wales for 1958*, Part III. Commentary. H.M.S.O., London.
[5] *Brit. med. J.*, 1960, **2**, 1373.
[6] Dameshek, W., *J. Amer. med. Ass.*, 1960, **174**, 1853.
[7] Wilson, C., *Practitioner*, 1956, **176**, 14.
[8] Sutherland, J. M., *A.M.A. J. Dis. Child.*, 1959, **97**, 761.
[9] Bretschneider, R., Stur, O., and Zweymüller, E., *Disch. med. Wschr.*, 1960, **85**, 1444.
[10] Beveridge, J., *Med. J. Aust.*, 1961, **1**, 93.
[11] Burns, L. E., Hodgman, J. E., and Cass, A. B., *New Engl. J. Med.*, 1959, **261**, 1318.
[12] Weiss, C. F., Glazko, A. J., and Weston, J. K., *ibid.*, 1960, **262**, 787.

to suppress infection preparatory to lobectomy for bronchiectasis? This is only one field of use; the treatment of intestinal infections less serious than typhoid fever, of infections of the skin and the urinary tract have all to be considered too. If Dameshek's words are to be taken literally, the only conditions in which chloramphenicol should be used are those "in which no other antibiotic is currently effective." Then almost all uses are excluded, because in fact there are more or less effective alternatives to chloramphenicol for dealing with almost any bacterial species causing human infections. It would be helpful if an authoritative pronouncement could be made which translates Dameshek's warning into more precise terms.

A different kind of toxic effect from chloramphenicol has recently come to light. Apparently it had become a common practice, particularly in the United States, to administer chloramphenicol to newborn infants, whether full term or premature, in whom there was some reason to fear infection. Apart from prematurity itself, birth more than 24 hours after rupture of the membranes is mentioned as an indication for this treatment. The drug has been given intramuscularly in inexplicably large doses, as high as 160 mg. per kg. daily, which is the equivalent of about 10 g. to an adult. The effect of this is sometimes to produce the "grey syndrome," a circulatory collapse usually followed by death in a few hours. J. M. Sutherland[8] describes three cases and R. Bretschneider and his colleagues,[9] of Vienna, five others, of rather different nature because there were more definite indications for antibiotic treatment such as major operations for congenital defects. A single fatality from the same cause has recently been reported from Australia by J. Beveridge.[10] L. E. Burns and his colleagues[11] at the Los Angeles County Hospital conducted a comparative study to assess the risks of this treatment. Groups of 30–33 premature infants were given either no antibiotic, or chloramphenicol in a dose of 100–165 mg. per kg. daily, or penicillin and streptomycin, or all three of these antibiotics. The respective mortalities were 19, 60, 18, and 68%. Some estimations of chloramphenicol in the blood showed levels rising to as high as 170 μg. per ml. C. F. Weiss and colleagues[12] have since shown that in the newborn infant the capacity both to conjugate chloramphenicol and to excrete it is incompletely developed; they consider that the dose in the premature and full-term infant should not exceed 25 and 50 mg. per kg. respectively. All these authors seem to assume that chloramphenicol given prophylactically to newborn infants serves a useful purpose, but none of them offers any evidence of this. It would be interesting to know how many infants in the untreated group in the Los Angeles series developed infections which were prevented—if indeed they were—with such losses in the treated, but on this aspect of their study these authors are silent.

50TH ANNIVERSARY OF BIOCHEMICAL SOCIETY

The Biochemical Society celebrated its fiftieth anniversary last week by holding a symposium on "The Structure and Biosynthesis of Macromolecules" in the Senate House, University of London.[1] An internationally distinguished group of speakers discussed nucleic acids, polysaccharides, and proteins under this general heading, and the Third Hopkins Memorial Lecture was given by Sir Hans Krebs on "The Physiological Role of the Ketone Bodies."

For many of our older readers education in what is now called "biochemistry" may have been confined to a few lectures on "chemical physiology" given either as a part of the general course in physiology or as a coda to a course of lectures on organic chemistry, most of which seemed to be little related to medicine. Biochemistry is now recognized by the G.M.C., alongside anatomy and physiology, as an integral part of the preclinical medical curriculum. Yet it may be doubted if we in Great Britain are, in general, aware of the change that has come over medical education in some other countries, where biochemistry now looms as large as anatomy used to do. This is perhaps surprising in a country where biochemistry has so conspicuously flourished in recent years.

Readers can hardly pick up a copy of the *Journal* these days without finding references to, for example, the use of plasma enzymes as diagnostic aids, therapy based on antibiotics and other antibacterial substances, inborn errors of metabolism as the basis of disease—all subjects which have developed not only within the life of the Biochemical Society, but especially within the past twenty to thirty years. During the Society's life many vitamins have been born, argued about, isolated, and synthesized, passing successively through the stages of hypothetical entities and excessively rare substances, finally to become commonplace preparations in the catalogues of the pharmaceutical houses. Many hormones have gone or are going through a similar evolution, and indeed the steroid hormones, largely available by conversion of commonly occurring steroids, are now accompanied by many artificially produced relations which mimic or antagonize the actions of the natural substances. There are also potent materials only distantly related chemically to the naturally occurring biologically active substances whose action they show, of which diethystilboestrol

[1] A report of the proceedings will be published later.

(or stilboestrol as it is now commonly called) was the forerunner. These many substances are of great value in the treatment of disease. The number of chemotherapeutic agents now available is almost embarrassing, while the number of drugs in use which influence behaviour is increasing rapidly. The volume of literature from the pharmaceutical houses about their new products is in itself eloquent material tribute to the tremendous impact that the growth of biochemical knowledge has had on medicine.

The realization that nucleic acids enter into the constitution of genes on the one hand, and viruses on the other, has opened up disturbing possibilities for the use of artificially produced nucleic acids. Knowledge of the chemical basis of virus mutation and the ability to alter artificially genetic characters of complex organisms are two of the possibilities that may well emerge. It is natural that the symposium with which the Biochemical Society celebrates its fifty years of life should open with a discussion of nucleic acids, since these themselves control the chemical constitution, and therefore the biological activity, of the enzyme proteins on which all life depends.

Where is all this leading to? Nobody could confidently predict what medicine will be like when the Biochemical Society celebrates its centenary. Nevertheless, it seems certain that training for medicine then will include much more biochemistry than it does now, even though some cherished subjects in the medical curriculum must give way to make this possible. Should this happen sooner?

"PRESCRIBERS' JOURNAL"

Virtually since the beginning of the Health Service the amount paid out on drugs has caused agitation. The reasons for this are numerous and well known, for they receive a frequent airing in the columns of daily and weekly newspapers. On the one side is a drug industry deservedly eager to sell its products; on the other is a somewhat ambivalent taxpayer, slightly resentful at his tax bill but eager for his bottle of medicine. In between stands the unfortunate doctor, shot at from all sides. As he is well aware, a considerable official team exists to give advice, encouragement, criticism, warnings—and worse—while he edges along the tight-rope of economical prescribing. The *British National Formulary*, the Cohen committee, regional officers from health departments, local medical committees—all are there to help him on his way and to catch him, sometimes not very gently, if he falls off. In addition, the Ministry of Health has for some years been publishing *Prescribers' Notes* to give detailed guidance on the costs of drugs in current use, and several journals widely read in Great Britain publish "authoritative notes giving practical and unbiased guidance on new drugs and new formulations of older drugs." Despite all this the final report of the Hinchliffe Committee[1] (from which the quoted words are taken) recommended that a new journal should be established "to distribute to general practitioners up-to-date information about new drugs and preparations and the results of clinical trials." Consequently, the money was found, and this week the first issue of *Prescribers' Journal* appears. It is issued free, every two months, by the Ministry of Health and the Department of Health for Scotland to all doctors in the Health Service and to medical students in their clinical years; copies are also obtainable for 6d., post free. *Prescribers' Notes* is to be discontinued.

The Hinchliffe Committee was somewhat confused in its recommendations about the manner in which the new journal should be published, saying at one point that it should be "independent of the pharmaceutical industry and of the Ministry of Health" and a few lines later that it should be "published and distributed by the Ministry of Health, who might also be asked to pay for the editorial organization." In the upshot the second course seems to have been followed in the main, but with assistance from outside the Ministry (and Scottish Department). A committee of management under Professor M. L. Rosenheim includes two professors of pharmacology and therapeutics as vice-chairmen, four general practitioners, and officials from the English Ministry and the Scottish Department of Health. Associated with these is an advisory panel of experts comprising ten professors and one distinguished non-professorial physician. The editor himself, Dr. J. L. Hunt, will thus not lack expert guidance, and he deserves congratulations on the appearance of the first issue. The three subjects chosen for discussion in it (two in signed articles) are griseofulvin, topical corticosteroids, and penicillins. If none are particularly new, they certainly engage the family doctor's attention often enough.

According to the Ministry of Health, "it has not proved practicable to arrange for the journal to be produced in the way suggested by the (Hinchliffe) Committee,"[2] and, oddly enough, the copy sent for review nowhere states plainly who published or printed it. It sets out "to provide the doctor with early and reliable information about new pharmaceutical products."[3] This is a tall order—even for a periodical launched under Government auspices at public expense—but if it can be fulfilled *Prescribers' Journal* will serve a useful purpose. The Hinchliffe Committee believed that the average doctor is unable to judge the validity of the claims made by the manufacturers' representatives on behalf of the innumerable new drugs that are produced, and certainly, if practitioners were quickly supplied with information about new drugs and preparations as they become available, doctors would be less likely to be susceptible to propaganda. But what really makes for good prescribing—which is not always the same as economical prescribing—"is sound undergraduate education in therapeutics and continued postgraduate reading and courses throughout a doctor's working life."[4]

[1] *Final Report of the Committee on Cost of Prescribing*, 1959. H.M.S.O., London. 6s. net.
[2] Ministry of Health, E.C.L.25/61.
[3] *Prescribers' Journal*, 1961, **1**, 1.
[4] *Brit. med. J.*, 1959, **1**, 1285.

COLLAPSE FROM RESERPINE

In the past few years reserpine has been shown to reduce levels of catecholamines (chiefly noradrenaline) in the stores of the peripheral sympathetic nervous system.[1-3] As a result of this depletion of the adrenergic mediator from the postganglionic sympathetic nerves the stimulant effects of these nerves on the heart are greatly reduced or abolished.[4] Sympathetic peripheral vasoconstriction is similarly reduced. Although reserpine may transiently decrease the discharge of central tonic sympathetic impulses,[5] this discharge is normal or possibly slightly increased during most of the time that the drug is exerting a hypotensive effect.[6] Thus the present view is that the hypotension due to reserpine is caused by a peripheral block of the sympathetic nervous system due to depletion of its adrenergic mediator and that the decrease in central discharge plays a transient role at most. Syrosingopine[7] and deserpidine probably act similarly. Although reserpine itself disappears rapidly from the body,[8] the depletion of noradrenaline lasts about a fortnight. This leads to a feature not seen with most drugs, since they usually act for much shorter times. When reserpine is given in repeated doses, even if the doses are 24 hours apart, enough residual effect persists from the previous dose to lead to a cumulation of effect[9] (as with the glycosides of digitalis). Because of this cumulation, repeated administration greatly reduces the dose required for a given effect; in fact, the depletion of noradrenaline and the resultant interference with sympathetic function can be produced in dogs by dosage schedules comparable to even the lowest used clinically in man.[4] Depletion of human stores of catecholamines has not been studied. Excretion of noradrenaline is reported to be reduced,[10] but no data are available to determine the lowest effective dose. However, there is probably little species difference in sensitivity to reserpine between man and dogs, since reserpine produces hypotension in man at dose levels similar to those which produce a comparable hypotension in dogs. Therefore, for safety, reserpine must be regarded as capable of depleting human stores of noradrenaline at all doses used clinically, when given for some time, until proved otherwise.

Patients on reserpine should be treated as potentially "poor risks" when their cardiovascular systems have to cope with an increased load of work—for example, during labour, electroshock therapy, or anaesthesia and surgery. Probably only rarely will the load be so severe, the depletion of noradrenaline so great, or the circulatory reserve so low that the cardiovascular system will collapse under the load. Nevertheless the possibility exists. There is already some evidence that difficulties of this nature have arisen in patients under treatment with reserpine. C. S. Coakley and colleagues reported twenty-four cases of fall in arterial pressure during anaesthesia in patients on rauwolfia therapy.[11] In another case the arterial pressure fell alarmingly during induction of anaesthesia; the operation was therefore postponed two weeks, during which the patient's rauwolfia therapy was discontinued, and then the procedure was carried out uneventfully by means of the same anaesthetic agents as were tried originally. Reserpine was clearly responsible here. In other cases —for example, a recent case of fatal hypotension in late pregnancy after large doses of reserpine,[12] or five cases of ankle oedema and basal rales occurring a week after reserpine therapy was begun and ceasing when it was stopped[13]—though reserpine cannot be blamed with certainty, it has not been ruled out as the cause. Until the data needed to exonerate or incriminate reserpine positively become available, this drug and its analogues are best given with due caution in these circumstances and preferably discontinued two weeks before labour, elective surgery, or electroshock therapy.

[1] Carlsson, A., Rosengren, E., Bertler, Å., and Nilsson, J., in *Psychotropic Drugs*, p. 363, edited by S. Garattini and V. Ghetti, 1957, Amsterdam.
[2] Krayer, O., and Fuentes, J., *J. Pharmacol.*, 1958, **123**, 145.
[3] Burn, J. H., and Rand, M. J., *Brit. med. J.*, 1958, **1**, 903.
[4] Blinks, J. R., and Waud, D. R., *J. Pharmacol.*, in press.
[5] Bein, H. J., *Ann. N.Y. Acad. Sci.*, 1955, **61**, 4.
[6] Iggo, A., and Vogt, M., *J. Physiol.*, 1960, **150**, 114.
[7] Orlans, F. B. H., Finger, K. F., and Brodie, B. B., *J. Pharmacol.* 1960, **128**, 131.
[8] Sheppard, H., Tsien, W. H., Plummer, A. J., Peets, E. A., Giletti, B. J., and Schulert, A. R., *Proc. Soc. exp. Biol. (N.Y.)*, 1958, **97**, 717.
[9] Waud, D. R., Kottegoda, S. R., and Krayer, O., *J. Pharmacol.*, 1958, **124**, 340.
[10] Gaddum, J. H., Krivoy, W. A., and Laverty, G., *J. Neurochem.*, 1958, **2**, 249.
[11] Coakley, C. S., Alpert, S., and Boling, J. S., *J. Amer. med. Ass.*, 1956, **161**, 1143.
[12] Nardone, A. A., Stroup, P. E., and Gill, R. J., *Amer. J. Obstet. Gynec.*, 1960, **80**, 258.
[13] Perera, G. A., *J. Amer. med. Ass.*, 1955, **159**, 439.

NEEDS OF OLD PEOPLE

The Ministries of Health and Housing and Local Government have issued a joint circular[1] in which they urge housing, local health and welfare authorities, and voluntary organizations to co-operate in ensuring that elderly people get what they need. This is a well-worn theme, but it has need of repetition. There could be a much wider exchange of ideas between the various departments of local authorities and the general practitioners and geriatric departments in their districts. The necessity for homes specially designed for old people, sometimes in groups with a warden able to give some individual help, is mentioned once more. In spite of some advantages of the idea, the Ministries rightly warn against too much grouping of old people's dwellings round the local authority's homes after the Scandinavian pattern, for this would create isolated colonies and new difficulties. The circular outlines again the services likely to be needed for old people, especially home helps and the provision of meals for those alone or incapacitated, but there is nothing new or arresting here to stimulate those authorities who provide too little of these essential services.

The thirteenth annual report[2] of the National Corporation for the Care of Old People has appeared at the same time. This reviews the aims and achievements of the corporation, but also critically surveys the wider scene which the Ministries' circular attempts to cover. The meals-on-wheels service, so vital but so difficult a service to run on its present lines, provides on a national average only two meals a week for the

[1] *Services for Old People*, Circular No. 10/61 (Ministry of Housing and Local Government); Circular No. 12/61 (Ministry of Health).
[2] National Corporation for the Care of Old People. Thirteenth Annual Report for the Year Ended September 30, 1960. Nuffield Lodge, Regent's Park, London N.W.1.

people it serves, which is far too little. The corporation thinks that perhaps new legislation may be required to place the responsibility for this service on local authorities. The rate of building of the special types of housing advocated by the circular generally speaking lags far behind what is needed, and the corporation charges the Ministry of Housing and Local Government with not realistically assessing future needs. The corporation finds, too, that 85 out of 188 responsible local authorities have provided less than one bed per 1,000 of population in small welfare homes, and only 29 have reached the recommended figure of two per 1,000 of population. The corporation's report expresses misgivings, which have been voiced elsewhere, about the quality of care in some private homes for elderly people, and points out how difficult is proper inspection and control even under existing legislation.

Local authorities and their officers—and perhaps also the Ministries—are not always aware of the way in which the elderly population is changing. Older people are now surviving to the extremes of life; they are as a group becoming increasingly frail, and they therefore need more personal attention. This trend is already quite clear, and it is throwing unforeseen stress upon existing homes, whose pleas for more staff, adaptations, and re-equipment are not always well received. It will inevitably increase the demand for places in local-authority homes, and it should affect the design of new homes for the future. Moreover, many authorities are providing most comfortable small homes for selected residents, but very few are realistically assessing the needs for the many physically handicapped, mentally backward, and socially less acceptable old people who are also their responsibility. Contrary to the Ministries' hopes, increasing infirmity among tenants and residents of homes is to be expected. There is even the risk that places provided for the old will go to younger people for lack of "suitable" elderly applicants. It is wrong that old people are forced to seek refuge in over-burdened hospitals on grounds of frailty alone, but this is what occurs.

CHOLESTATIC HEPATITIS

The histological appearance of the liver in the acute stage of infectious viral hepatitis usually shows a remarkable uniformity. The lesion is a diffuse one of necrosis and regeneration of the liver cells associated with a moderate degree of mononuclear-cell infiltration within both the lobules and the portal tracts. In this, the so-called classical, form of the disease the histological evidence of bile stasis, in the form of bile staining of liver cells and plugs of inspissated bile in the intralobular ductules, is inconspicuous. In well under 10% of cases, however, the histological appearance is much more like that of an extrahepatic biliary obstruction with little sign of damage to parenchymal cells but considerable evidence of bile stasis. How and why this difference is brought about has not so far been satisfactorily explained. A recent study by I. N. Dubin and his colleagues[1] of a local epidemic in Texas affords strong evidence in favour of a variant virus with an unusual predisposition to induce this cholestatic form of the disease.

Ninety-three patients with a clinical diagnosis of infectious hepatitis and subjected to a liver biopsy within 21 days of the onset of jaundice were available for study. On the basis of the relative proportion of parenchymal damage to bile stasis these were divided into 67 cases of classical hepatitis and 26 cases of cholestatic hepatitis, an incidence of almost 28%. When these same patients were classified by both immunological type (that is, infectious or serum hepatitis) and geographical area in which the disease had probably been contracted, it was found that no fewer than 21 of the cholestatic cases occurred among the 46 patients who were local residents—that is, an incidence of nearly 46%. The remaining 5 cases were found among the 30 patients returned from Korea with a diagnosis of serum hepatitis.

A bacteriological and virological study of the biopsy specimen on 14 cases chosen at random from the 93 was entirely negative. As only one of the 14 belonged to the cholestatic category, no conclusion could be drawn on the micro-organisms causing the two varieties of the disease. The histological differences, however, were certainly not attributable to differences in the stage of the disease at which the examinations were made, nor could they be attributed to any obvious differences in constitution of host or administration of hepatotoxic drugs. Dubin and his colleagues have therefore concluded that the remarkably high incidence of cholestatic hepatitis in the Texan epidemic was most probably due to a peculiarity of the causative agent. The epidemic of hepatitis in Delhi[2] in 1955 in which 57% of the patients were reported as having the cholestatic form of the disease supports the view that a special variant of the hepatitis virus is responsible.

Is the different effect of these variants due to a different type of injury to the parenchymal cells, or do they act on different anatomical constituents, the liver cell in the one instance and intrahepatic bile channels in the other? The evidence previously presented by Dubin[3] favours the former interpretation. According to that view the motive force for the flow of bile through the liver is the secretory force of the parenchymal cells. When these cells are severely damaged, as in classical hepatitis, cholestasis is slight because little bile is being secreted. When the cell damage is slight, stasis is considerable because the pressure of secretion is presumably insufficient to overcome the normal resistance of the bile capillaries. The inverse relationship often observed between the severity of cell damage and bile stasis may thus be explained without postulating damage of some ill-defined "cholangiole."[4]

Sir Robert Platt, Bt., was re-elected President of the Royal College of Physicians of London on March 27.

[1] Dubin, I. N., Sullivan, B. H., jun., Le Golvan, P. C., and Murphy, L. C., *Amer. J. Med.*, 1960, **29**, 55.
[2] Smetana, H. F., in Henry Ford Hospital International Symposium, *Hepatitis Frontiers*, 1957, edited by F. W. Hartman *et al.*, p. 77, Boston.
[3] Dubin, I. N., *Gastroenterology*, 1959, **38**, 645.
[4] Watson, C. J., and Hoffbauer, F. W., *Ann. intern. Med.*, 1946, **25**, 195.

STIMULATION OF NEW DISCIPLINES IN GENERAL PRACTICE BY TAPE-RECORDED TALKS

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Our fathers and grandfathers in general practice had many contacts with hospital life, and were able to keep in touch with new ideas as they developed. Unfortunately, the separation of general practice from hospital medicine coincided with an unprecedented increase in the number and rapidity of advances in treatment. The ennui with their job felt by many general practitioners to-day is often due to inability to absorb and remain interested in so many new ideas. There are those who believe that the true "family doctor" cannot and possibly even ought not to continue to exist, but others, like the College of General Practitioners, believe that what is needed is a fresh attitude to this problem of keeping up to date, by means of creative activity such as research and active as well as passive education. There are plenty of good formal courses, but the doctor is fortunate who can attend them more than biennially. Good general practitioners will do their best to go to courses, but many difficulties confront them, chiefly the problem of providing a deputy and the need to book a long time ahead. Of 1,000 members replying to a recent College questionary, 512 had attended a formal course in the last two years, but even the best course cannot keep a doctor aware of all the advances during that time.

The good general practitioner of the past could find an outlet in hospital work, but this is less easy for him now. He may well spend some years improving his practice and building better surgery premises, but he has little incentive to improve his standard of work and knowledge. It is very easy, once ten to fifteen years have passed by, to slip into complacent apathy, to continue to use the clichés of the past. Asher (1959) in his Lettsomian Lectures warns us against accepting current beliefs as facts merely because everyone believes them, and we in general practice must beware of going on believing things that once were "facts" but are now no longer accepted. Research can bring that new interest that leads us to want to find out more, and clinical assistantships may restore contact with hospital, but there remains the need for perpetual re-education.

Academic Isolation

In 1958 we wrote about the "academic isolation" of the general practitioner and its possible causes and cure (Graves and Graves, 1958). We felt that these general practitioners had lost their way among so many advances and that they had lost the capacity to keep up to date by means of reading alone; and we thought that the use of sound and of audio-visual methods, and group discussion of problems, would help them to find the way back. We wrote to 50 doctors in isolated country practices, asking if they would like to take part in an experiment in the use of talks recorded on tape and long-play disks. Twenty-seven of them agreed to take part, and the success of the experiment led us to expand the scheme; and since April, 1958, the Medical Recording Service has sent out six recorded talks a year to its listeners, who now number over 300 in the United Kingdom and many more overseas. These talks (each lasting about 30 minutes) are sent round "circuits"—groups each of 10 doctors who pass the recordings from one to another, the last man returning them to us. The six circuit talks are supplemented by a library of other talks on loan on demand. Wherever possible the talks are illustrated by transparencies or diagrams.

Because we were interested in the idea of academic isolation and the need for contact with others, we urged listeners to collect others to discuss the talk with them if possible; but we had not expected the scheme to gather impetus in the way that it did and to develop firmly along its own lines.

Development of Discussion Groups

The first 27 listeners were *invited* to take part, but (with few exceptions) all the others were volunteers. The early listeners invented the circuit system and the discussion tapes on which listeners themselves record questions and comments, and they have suggested many other administrative ideas as well as subjects, titles, and speakers. From the beginning we have found listeners interested enough to want to help us to improve the service.

In June, 1959, we sent out a questionary to discover how many listeners were holding meetings, and how many were being encouraged to read more (Graves and Graves, 1959). 61% of the 161 listeners at that time were meeting more often than before, 51% had looked up subjects after the talks, and 40% had followed up subjects later in the journals. Another interesting finding was that, whereas *before* joining circuits 65% never held meetings with local colleagues, *after* joining only 8.5% still never did so. These figures showed that most circuit members were becoming aware of the advantages of listening in company. They were meeting, more or less regularly, to hear and discuss talks of which the titles were not previously disclosed except that they would be on subjects of general interest. Last year's titles were: "Cortisone," by Dr. R. I. S. Bayliss; "Advances in the Treatment of Burns," by Mr. D. N. Matthews; "Early Diagnosis of Deafness in Young Children," by Dr. Mary Sheridan; "Some Medical Emergencies," by Dr. C. Allan Birch; "How to Read Medical Journals," by Dr. Hugh Clegg; and "Are Colds Catching?" by Dr. R. E. Hope-Simpson. Copies of these have been sent to all circuit members and have now been heard by about a thousand doctors in this country. (We have no accurate figures about overseas listeners.)

The library titles cover many subjects, as varied as heart sounds, shingles, and psychiatry. During the 12 months from January 1 to December 31, 1960, 680 copies of talks were sent out on loan from the library, of which 280 were tapes, 333 disks, and 67 tapes or disks sent to overseas members.

In this way we hoped in the course of time to cover some of the advances in all the main subjects, and to discover for listeners their unsuspected gaps in knowledge. In the early days of the service we found that if we used the library rather than the circuit system few members would deliberately ask for subjects other than those in which they were particularly interested and so probably already fairly well informed,

and that they might often be unaware of advances in other subjects. Experience has suggested six as the optimum number of circuit recordings a year, which can be supplemented by more from the library if listeners want them.

Emergence of Different Kinds of Groups

Soon we noticed that we were getting inquiries from doctors in no sense isolated. One member from Edinburgh, one of the best places for postgraduate education, said that for him to go on a course meant leaving his young family every Sunday (his only real day off) for 12 weeks. Another, who was able to go to many courses, said that he liked the new approach of the recordings. There was now, it seemed, an air of apology about those who could *not* hold meetings.

Since the beginning of the service we had collected figures about the number of playings of each talk and the number of listeners at each playing, from which a rather arbitrary "listening index" could be worked out in each case. In the early days most indices were around 2, and this figure crept to 3.1 for both library and circuit talks, showing that by mid-1959 three doctors listened at each playing. Recent figures suggest a divergence between groups of a few partners or friends meeting casually when a recording arrives and listeners who have developed proper study groups, meeting specially for the purpose, sometimes on prearranged series of dates for which talks might be reserved in advance. Recordings are now no longer the sole *raison d'être* of these groups, as cases may also be discussed or local consultants be asked to speak. More figures are being collected about the composition of these groups.

An important new development is the "Journal Club" (Graves and Graves, 1960). Members of these clubs, as well as discussing recordings, each make a study of a particular journal, from which they prepare abstracts to read and discuss with one another at their monthly meetings. In such serious study groups we have the complete cycle of audio-visual education helping general practitioners to revive interest in the printed word. Two interesting aspects of these groups are that each member is necessary to the others—he cannot just sit and listen, but has a real part to play in his own and the others' education; and that they show that it *is* possible for general practitioners to find the time and enthusiasm for serious study of this kind.

Intrinsic Educational Value of Sound

It is probable that sound and audio-visual methods of education have many real advantages over the purely visual in some circumstances, but this should not be overemphasized. The spoken word may fix something in the mind and kindle interest in the reading that must still play the greater part. Joyce and Weatherall (1957) found that students (of pharmacology) learned better from auditory teaching than from reading alone; and it is possible very soon to become weary, like Alice, of a continuous diet of "books with no pictures and no conversations."

Some subjects, of course, lend themselves particularly well to auditory teaching, such as, for instance, heart sounds and conditions affecting the voice, and we are beginning to collect a reference library of medical sounds. Lloyd (1959), describing the voice in myxoedema in a written article, had to describe the qualities of harshness at much greater length than in a talk he made for us, in which he played recordings of patients before and after treatment.

But, apart from subjects like these, sound has no special value, no special magic of its own—the magic lies in the voice of the speaker and what he has to say, and how he says it. There is certainly no virtue in reading aloud words and figures written for print—indeed, it is quicker to read from the page; nor is there now any novelty in recording, as there was in our experimental days. Talks written for recording, we find, should be quite different from those intended for the lecture hall, as well as from those written for the journals. After three years of recording and studying listening indices the picture of what the general practitioner wants is becoming clearer to us. Fine points of detail, and figures, are best given as diagrams, which can be studied again later. A speaker referring briefly to a general field of advance, with more detail about some aspect of it in which he is particularly concerned, is preferred to the speaker who tries to cover too much ground at once. The important thing is to draw attention to, and arouse interest in, new ideas, so that listeners may be stirred to read about them.

Illustrations are appreciated, as are speakers who can explain them well. We like to bring well-known speakers to talk of their own work to doctors who would have little chance to hear them in person (and, of course, one day to doctors not yet born). But the magic quality that a good speaker has of contact with his audience is by no means confined to the famous, and every effort should be made to search out the possessors of this most valuable gift. Perhaps we should add that our speakers are always named, and always read their own talks, which are usually specially commissioned for the purpose.

Conclusion

The interest aroused by the recording service does suggest that there was and still is a great need among general practitioners for active participation in some way in group education. Who are our listeners? The total audience in this country in December, 1960, was something over a thousand general practitioners, and an unknown number overseas. Branches of the service are thriving in New Zealand, South Africa, and Israel, and small groups in other places abroad. Other organizations, some of whom have studied our methods, are starting libraries and publications in sound.

We know a few facts about the 308 members of listening circuits in the U.K. at the present time: the average "age" is 16 years since qualification, and most are in the groups 5–10, 10–15, and 15–20 years since qualification. The average listener, then, has been in general practice for more than 10 years and has had time to settle down—but not into a rut. It is perhaps interesting that 86 of the 308 have higher qualifications, comprising 41 D.Obst.R.C.O.G., 22 M.D., 12 D.C.H., 7 M.R.C.P., 6 D.P.H., 3 F.R.F.P.S., 2 F.R.C.S., one D.I.H., one D.A., and one F.R.C.P., and 60 have written articles in medical journals.

Many of them will have entered general practice following a father's example, and some may be fortunate enough to have been inspired by a good general practitioner as student or trainee. Others have been registrars and know the discipline of academic competition. They have in common a desire to improve

their work as doctors and to maintain knowledge and interest in new ideas as they develop, so that they will not become bewildered as their hospital days recede into the past. Membership of a study group of any origin means that a searching light is turned on to one's own deficiencies, and the self-examination that results may be as valuable as the few crumbs of knowledge that linger from hearing the talks. Ideas for research, or for improvements in practice, often begin in friendly discussion, and the feeling of fellowship in a common problem must encourage friendly co-operation between neighbours who might have been nothing but rivals.

Summary

The work of the medical recording service of the College of General Practitioners since its experimental beginning in 1957 is discussed, and the development of different kinds of general-practitioner study groups is described. Suggestions are offered on the value of audio-visual methods in the postgraduate education of general practitioners.

We are grateful to Smith Kline and French Laboratories Ltd. for their appreciation of the value of recorded medical talks when we first experimented with them in 1957, and for their continuing generosity since that time in making a grant to the College to cover the expenses of the recording service. These recordings are now available to non-members.

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CLINICAL ASPECTS OF GENETICS

ROYAL COLLEGE OF PHYSICIANS OF LONDON

[FROM SPECIAL CORRESPONDENTS]

A two-day conference on Clinical Aspects of Genetics was held at the Royal College of Physicians of London on March 17 and 18. The conference was intended primarily for fellows and members of the College who are consultants in medicine or pathology.

First Principles

The President, Sir ROBERT PLATT, welcoming the participants, said that clinical genetics had been an abiding interest of his own throughout his career. Dr. J. A. FRASER ROBERTS (London) then reviewed the principles and methodology of human genetics. He described briefly the morphology of the 23 chromosome pairs in the normal cell nucleus and the process of somatic division. With the aid of illustrative pedigrees he defined dominance, recessiveness, and sex-linkage, pointing out the importance of consanguinity in recessive inheritance and describing methods by means of which heterozygous carriers of certain recessive genes could be identified. He also discussed degrees of penetrance of genes and multifactorial inheritance, and pointed out that, as occurs in deaf-mutism, different genes might have an identical clinical effect.

In the subsequent discussion the PRESIDENT and Professor J. MCMICHAEL (London) raised the question of the multifactorial inheritance of hypertension and pointed out several difficulties which arose in studying the genetic aspects of this condition. Dr. C. A. CLARKE (Liverpool) asked why detrimental genes remained dominant; Dr. FRASER ROBERTS replied that mutation seemed in many instances to replace genes lost when affected individuals failed to reproduce. Dr. J. MARSHALL (London) raised the question of genetic counselling in first-cousin marriages, and Dr. FRASER ROBERTS replied that recent statistics from Japan showed clearly the risks of first-cousin marriages compared with controls.

Muscular Dystrophy

Dr. J. N. WALTON (Newcastle upon Tyne) then discussed the genetic aspects of muscular dystrophy and related disorders. He gave reasons for suggesting that in 90% of cases the Duchenne (pseudohypertrophic) variety of muscular dystrophy was due to a sex-linked recessive gene and in 10% to an autosomal recessive. Limb-girdle dystrophy was usually transmitted as an autosomal recessive, less often as a dominant and very rarely was it sex-linked, while facioscapulo-humeral dystrophy was usually dominant but occasionally recessive. He then reviewed the inheritance and interrelationship of myotonia congenita, paramyotonia, and dystrophia myotonica, all of which were usually dominant traits. The same mode of inheritance usually obtained in the different varieties of periodic paralysis, but many of the less common metabolic myopathies (e.g., the McArdle syndrome) as well as some of the congenital non-progressive group of myopathies were usually recessive.

Schizophrenia

Dr. E. T. O. SLATER (London) considered the genetic aspects of mental disease and said that he would concentrate upon schizophrenia. He said that schizophrenia was found in 8% of the sibs of affected individuals, whereas the expected incidence in the general population was only 0.8%, but there was no clear evidence to suggest that the inheritance of the disease followed a simple Mendelian pattern. There was, however, a high degree of concordance in twin pairs. The genetic pattern did not appear to depend upon the clinical variety of the illness (catatonic, hebephrenic, paranoid). He went on to review carefully the evidence which seemed to exclude the possibility that the disease was due to a single recessive gene with incomplete penetrance; equally the statistics did not favour the possibility of incomplete penetrance of a single dominant gene. Everything seemed to indicate that the clinical condition was seen in some homozygotes and in some heterozygous individuals, so that the responsible gene was probably of intermediate character, midway between dominance and recessivity.

Congenital Malformations

Dr. C. O. CARTER (London) then considered congenital malformations, which appeared to be responsible for about one-quarter of all infant deaths, though statistics varied for different parts of the world. He carefully reviewed the evidence which suggested that pyloric stenosis in infancy was probably due to sex-linked dominant multifactorial inheritance. Whereas in the case of cleft palate both genetic and environmental factors were involved, in harelip the low incidence of the condition in second-degree relatives as well as other evidence suggested sex-modified multifactorial inheritance of the condition. He also considered in detail the interplay of genetic and environmental factors which were responsible for congenital dislocation of the hip. Acetabular hypoplasia (probably multifactorial) and generalized joint laxity (dominant) often occurred together to give hip dislocation, and the intrauterine posture of flexed hips and extended knees was an important contributory factor.

In the ensuing discussion, Dr. N. S. CLARK (Aberdeen) asked about the value of the serum aldolase in the diagnosis of muscular dystrophy and about the detection of carriers. Dr. WALTON replied that estimation of the activity of the serum aldolase was the most sensitive method of early diagnosis of the Duchenne-type dystrophy and could even be used to diagnose the disease in sibs of patients before clinical signs were apparent. However, an investigation of serum aldolase activity and of creatinuria in female carriers had been negative. Professor D. V. HUBBLE (Birmingham)

asked if the examination of relatives of children with pyloric stenosis revealed anything of note, and Dr. CARTER replied that the findings were essentially negative. Dr. R. W. PARNELL (Oxford) remarked that both parents of children suffering from harelip often showed a more striking degree of muscular development than did the average member of the population. Professor C. E. DENT (London) asked where mutations usually occurred, and Dr. J. FRASER ROBERTS (London) replied that they probably occurred in single germ cells rather than in a segment of ovary or testis.

Sex Chromosome Aberrations

The afternoon session was devoted to human chromosomes and their abnormalities in developmental disease. Dr. C. E. FORD (Harwell) dealt firstly with the technical problems of making suitable tissue preparations for the study of chromosomes, secondly with the description of normal chromosomes, and thirdly with the mechanisms whereby abnormalities of either chromosome number or morphology occurred. In particular he dealt with the technical aspects of marrow, skin, and blood culture, and he described the Denver system of classification of chromosomes. He drew attention to non-disjunction and anaphase lagging during gametogenesis as important sources of error in number, and to the mechanisms whereby translocations, duplications, and deletions occurred. Dr. FORD also defined chromosome mosaics, and dealt with the question of the numerical relationship between the number of X chromosomes in a nucleus and the number of sex chromatin-bodies.

Professor P. E. POLANI (London) described the sex chromosome abnormalities so far found in phenotypic females, and demonstrated how these fell into two general classes. Firstly, there were those associated with some or all of the features of Turner's syndrome, such as short stature, primary amenorrhoea, "streak" gonads, and neck webbing. In such individuals there was either a uniform XO sex-chromosome complement, or there was sex-chromosome mosaicism with one of the cell lines represented having an XO complement, e.g., XO/XX or XO/XXX mosaics. Finally, there were a number of instances where there was a morphological abnormality of one X chromosome, such as a deletion or the presence of an isochromosome for the long arm of the X chromosome. The second general class of abnormalities consisted of phenotypic females with more than two X chromosomes, e.g., those with sex-chromosome complements of XXX and XXXX. Professor Polani also introduced the topic of abnormal sex differentiation such as was shown in the syndrome of testicular feminization.

Dr. W. M. COURT BROWN (Edinburgh) presented a paper comparable to that of Professor Polani, but dealing with sex-chromosome abnormalities in phenotypic males. In particular he described the current views on their frequency in the general population.

Mongolism

Professor L. S. PENROSE (London) reviewed our present knowledge of the cytogenetics of mongolism. He paid special attention to the small group of mongols which deviated from the classical cytogenetic picture of mongolism, i.e., trisomy for autosome 21. The deviation was usually manifested by the presence of an abnormal translocated chromosome, in many instances formed from the fusion of an autosome 21 and one of the large acrocentric chromosomes. Often, but not invariably, these abnormal translocated chromosomes were to be found in one or other parent, usually the mother, and without producing any outward ill effects. The presence of the abnormal chromosome, however, increased the liability towards non-disjunction of No. 21 during gametogenesis, and consequently the liability towards the conception of mongols. The parent, of course, had a chromosome-count of 45, and the mongol child, who was effectively trisomic for autosome 21, a count of 46. Professor Penrose indicated how these unusual mongols, in the cytogenetic sense, accounted for a proportion of the mongols born to young mothers, and that often such mothers gave birth to more than one mongol.

Dr. M. FRACCARO (Oxford) concluded the session by drawing attention to other developmental abnormalities with a chromosome abnormality. Of these, the most important were trisomy 17, and a syndrome characterized by anophthalmia among other manifestations, which was associated with trisomy for one of the large acrocentric chromosomes, 13, 14, or 15.

Inborn Errors of Metabolism

On the second morning, Professor C. E. DENT (London) discussed the development of A. E. Garrod's idea that, similar to inherited malformations of the body, malformations of man's chemical make-up might also be inherited. Amino-acids, for example, were metabolized to urea and carbon dioxide by numerous steps of which we were usually unaware. Each of these steps was brought about by a particular enzyme, and if one of these catalysts was absent an intermediate product accumulated. Sometimes this metabolite was harmful: thus in alkaptonuria homogentisic acid caused ochronosis; and sometimes failure to arrive at the end-product was injurious as in albinism. Chromatographic analysis of the urine had been a powerful instrument in the investigation of metabolic errors. Normal urine contained traces of some 50 amino-acids.

Cystinuria was discovered by finding an intense cystine spot in the chromatogram. Even if no stones had been discovered clinically, one could always assume that some cystine deposits would be present in the kidney. In Fanconi's syndrome other amino-acids besides cystine were excreted in excess. If one of these was tyrosine the syndrome would include cirrhosis of the liver. The finding of phospho-ethanolamine would indicate hypophosphatasia, and large amounts of arginino-succinic acid were found in a familial condition which was associated with mental retardation and trichinosis nodosa ("dermatological for scruffy hair with knobs on"). Garrod had envisaged the actual absence of essential enzymes. It was possible that there was an enzyme polymorphism, and that abnormal mutants of the normal enzyme were formed as in haemoglobin synthesis. In xanthinuria xanthine oxidase must be present because this enzyme was responsible for the oxidation of hypoxanthine to xanthine, yet it did not convert xanthine into uric acid. This represented a "half enzyme abnormality." In phenylketonuria metabolites of indole amino-acids accumulated in addition to derivatives of phenylalanine. This suggested that excess phenylalanine blocked the metabolism of indole amino-acids. Garrod had been surprised that patients with cystinuria could metabolize cystine given to them by mouth. The abnormality here was one of renal transport.

Suxamethonium Sensitivity

Professor H. HARRIS (London) described familial suxamethonium sensitivity which was usually discovered when a patient responded to this short-term muscle relaxant with prolonged apnoea. Normally suxamethonium was destroyed rapidly by the pseudocholinesterase of the plasma. In these patients, and in some of their relatives, the enzyme level was low. When members of these families were grouped into presumed homozygotes and heterozygotes for the abnormality and into normal homozygotes a considerable overlap was seen in enzyme levels, but further biochemical classification could be made when pseudocholinesterase was inhibited by cinchocaine. The same concentration of cinchocaine caused 80% inhibition of the enzyme from normal homozygotes and 20% inhibition of the enzyme from abnormal homozygotes. With enzyme from presumed heterozygotes inhibition was about 60%. There was no overlap between these three groups, and when the pseudocholinesterase activity was low in a normal homozygote the inhibition was still 80%. One had to assume a polymorphism for two enzymes, of which one had a greater affinity to suxamethonium than the other. When another inhibitor was introduced—sodium fluoride—a third type of cholinesterase could be recognized.

Resistant Rickets

Professor C. BURNETT (North Carolina, U.S.A.) described the genetics of vitamin-D-resistant rickets. The abnormality was determined by a dominant sex-linked gene. If the propositus was a man, only his daughters were affected, but a woman could transmit the abnormality to sons and daughters. Sometimes individuals who had clearly handed on the abnormal X chromosome were themselves free from rickets. However, if hypophosphataemia was used as a more delicate indication of the disorder, "skipping" of generations could be eliminated. The gene was not fully dominant and men with a single abnormal X chromosome were more severely ill than heterozygous women. Many more women showed hypophosphataemia without bone disease than did men. To complete the study one would like to examine women who were abnormal homozygotes.

Dr. O. GARROD (London) drew attention in the discussion to hereditary diabetes insipidus which occurred only in boys. The condition was not fully recessive, and a high proportion of carrier women could be discovered by their subnormal response to nicotine and vasopressin. Dr. FRASER ROBERTS (London) drew attention to the importance of this test, as it enabled early diagnosis of affected boys. Delay in treatment might result in mental deficiency. In one case a child ended up with the psychiatrist before the diagnosis was made, because the boy was seen to drink from muddy puddles.

Abnormal Haemoglobins

Dr. H. LEHMANN (London) discussed the structure of human haemoglobin and how this was genetically determined. There were three independently controlled haemoglobins; the normal adult haemoglobin A, haemoglobin A_2 which normally did not amount to more than about 2%, and in infants the foetal haemoglobin F. The globin was formed of polypeptide chains, of which four were known. One, the α-chain, amounted to half the molecule in all three haemoglobins A, A_2, and F. The remainder was made up of β-chains in haemoglobin A, of δ-chains in haemoglobin A_2, and of γ-chains in haemoglobin F. There were two types of haemoglobin abnormalities. In α-chain deficiency surplus β-chains formed a tetramere β_4 or haemoglobin H, and surplus γ-chains formed γ_4 or haemoglobin Bart's. Alternatively the amino-acid sequence could be altered in any of the chains. When the α-chain was abnormal variants of haemoglobins A, A_2, and F were formed because all three haemoglobins contained α-chains. Mutations of the β-chain resulted only in variants of haemoglobin A, and of the δ- and γ-chains only in variants of haemoglobins A_2 and F respectively. As the four chains were under separate genetical control, inheritance of a haemoglobin with abnormality of the α-chain from one parent and of another with a β-chain abnormality from the other parent led to the formation of four adult haemoglobins in the offspring. There were the two parental haemoglobins and in addition the normal β-chains of the first and the normal α-chains of the second haemoglobin formed haemoglobin A, and the two abnormal chains combined to form a doubly abnormal pigment. In thalassaemia haemoglobin synthesis was inhibited. In one type the β-chain was affected and in another the α-chain. In β-thalassaemia only haemoglobin A production was involved and haemoglobins A_2 and F were formed in excess. In α-thalassaemia all three haemoglobins—A, A_2, and F—were affected. Tetrameres of the β- and γ-chains were produced, and though δ_4 had not yet been described haemoglobin A_2 was certainly not raised as it was in β-thalassaemia.

Heredity and the Alimentary Tract

The final session was opened by Dr. R. B. MCCONNELL (Liverpool), who discussed heredity and the gastro-intestinal tract. He first mentioned oesophageal carcinoma, usually sporadic but occasionally, as in two Liverpool families, controlled by a single dominant gene. He next discussed fibrocystic disease, a recessive disorder occurring only in Europe and having an incidence of 1 in 2,000 live births. This rather high frequency suggested that the 6% of the population who must be heterozygotes were at an advantage—possibly possessing resistance to some climatic or bacterial factor because of the abnormal chloride content of their sweat. He next discussed the association between duodenal ulcer and the ABO blood groups and secretor character. He pointed out that, if the population were made up entirely of secretors of A, B, and AB, there would be about 25% fewer ulcer patients than there were at present. Nevertheless, he emphasized that environmental factors must still be extremely important, and it would be interesting to study ulcer patients of different ABO and secretor phenotypes in relation to the amount of stress which they had encountered.

Genetic Advice to Patients

Dr. FRASER ROBERTS discussed genetic advice to patients. He said that the number requiring help was small and the majority sought information on conditions which had no clear-cut method of inheritance—spina bifida, anencephaly, talipes, harelip, and cleft palate being common examples. In these cases reassurance was usually justifiable, as the risks to further children were small. It was helpful to explain to parents that congenital malformations were accidents in development and that nothing in the habits of either parent was to blame. It should also be pointed out that the chance of any random mating producing a child with some defect was about 1 in 40. People appreciated odds, and advice should generally be given in these terms, the final decision with regard to having children always being left to the patients. Dr. Fraser Roberts stressed the importance of accurate diagnosis and thought that wherever possible affected individuals should be seen, though sometimes correspondence with the family doctor or a consultant might be sufficient.

Genetics and Neurology

Dr. R. T. C. PRATT (London) in a paper on genetics and neurology first discussed gargoylism. The principal features were mental deficiency, dwarfism, and corneal clouding, but by scoring for the presence or absence of 14 characters he found it possible to distinguish two forms of the disorder, one a sex-linked recessive and the other controlled by an autosomal recessive gene. He next referred to multiple neurofibromatosis and stressed the difficulty of accurately determining which patients had minor forms of the disease. He felt that more than six *café-au-lait* spots of not less than 1.5 cm. in their broadest diameter must be presumptive evidence of the presence of the condition. He then described most interestingly the syndrome of indifference to painful or noxious stimuli. Patients could be divided into those whose insensitivity was confined to pain and those in whom other forms of sensory loss were also present. In the first group the condition was probably a form of agnosia and no pathological changes were present in the afferent pathways; the second was more in the nature of a sensory neuropathy. In both, an increase in parental consanguinity suggested that there was a recessive method of inheritance. Dr. Pratt also mentioned another curious inherited character, that of ability to visualize number form, and he was very anxious to collect further examples of this rather unusual trait.

Complexities of Inheritance

Dr. C. A. CLARKE (Liverpool) discussed complexities of inheritance in man. He thought that the Rh polymorphism was extremely difficult to explain satisfactorily, since with every erythroblastotic death a heterozygote was eliminated. In the field of chromosome abnormalities he speculated whether fertile Turner individuals might not occur oftener than had hitherto been thought, the method of ascertainment tending to limit the discovery of cases to those who had amenorrhoea; furthermore, XO was often fertile in mice. He also thought that from the evolutionary angle it would be interesting to study the chromosomes of the great apes, the chimpanzee possessing 24 pairs. Referring to Dr. R. B. McConnell's paper on the association between duodenal ulcer and group O and non-secretion, Dr. Clarke pointed out that if the controls were unaffected sibs, not blood

donors, the significance of the association was much reduced. This he found perplexing, though perhaps insufficient sibships had been collected. Finally, he wondered whether genes always exerted their effect through enzyme action only—could the Hapsburg lip (apparently a dominant trait) be due to a single enzyme? Psychosomatic conditions with a strong inherited component—for example, bronchial asthma, with capriciousness as its main feature—were also difficult to explain. He wondered whether another Einstein could give us a new conception which would explain those partly inherited diseases where the mind–body relationship was so important and which were difficult of comprehension on the theory of genes being solely responsible for enzymes.

Dr. CLARKE and Dr. P. M. SHEPPARD showed an exhibit of butterflies and moths demonstrating basic genetic principles.

SYMPOSIUM ON RENAL DISEASE

ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH

The Royal College of Physicians of Edinburgh held a symposium on "Some Aspects of Renal Disease" in the Hall of the College on March 25. We report here a summary of the proceedings, which included Sydney Watson Smith lectures by Dr. J. S. ROBSON (Edinburgh) and Dr. J. P. MERRILL (Boston, Mass.). Dr. J. D. S. CAMERON, President of the College, presided.

Patterns of Renal Insufficiency

Dr. J. S. ROBSON took this as the subject for the first Sydney Watson Smith lecture. He pointed out that renal insufficiency was associated just as often with the loss of essential body constituents as with the retention of metabolites. Many discrete tubular syndromes were now recognized, but it was only recently that water-losing renal conditions had become susceptible to any systematization which took into account the hypothesis which implied that the kidney functioned as a single medullary organ with respect to water transport and related intrarenal water transport to the reabsorption of sodium in the loops of Henle and of urea in the collecting ducts. The effect of interfering with these two functions was illustrated by the concentration defects seen after mersalyl, in hyperparathyroidism, in potassium depletion, and in the newborn. In acute and chronic pyelonephritis which primarily affected the medulla, concentration defects tended to occur at an early stage and without nitrogen retention, whereas the polyuria of glomerulonephritis or hypertensive renal disease resulted from a urea diuresis and paralleled the reduction of filtration rate.

The evidence that renal ischaemia was the cause of tubular and cortical necrosis in acute renal failure was not entirely convincing. Recent studies of renal blood flow in these conditions, using radioactive krypton, gave values of 25–50% of normal, comparable to those found in severe congestive failure. However, estimates of renal blood flow made at the onset of acute renal failure were not available and there was much circumstantial evidence to support the ischaemic theory. The primary role of septicaemia with Gram-negative organisms in producing acute tubular necrosis had probably been underestimated, and in a series of sixty patients in Edinburgh there were fourteen in whom this seemed the most likely aetiological factor. Six of these were jaundiced. A coliform septicaemia might be the cause of many cases of the "hepato-renal syndrome," in which infection was the most important cause of mortality. The continued widespread use of prophylactic broad-spectrum antibiotics was contributing to this.

Other problems arising in these patients and in those with chronic renal failure were hyperkalaemia and acidosis. Dr. Robson described the mechanisms of these complications, and stated that the incidence of convulsions, cardiac irregularities, and death after dialysis was higher in severely acidotic patients. Rapid restoration of serum bicarbonate levels led to extracellular alkalosis due to continued hyperventilation. The stimulus for this hyperventilation was obscure, but, since bicarbonate ions did not penetrate cells rapidly, the intracellular *p*H might either remain the same or fall. This pattern was certainly seen after dialysis in the cerebrospinal fluid, into which bicarbonate ions passed only slowly. The acidity was not relieved.

The speaker discussed the place of intermittent dialysis in chronic renal failure using an exteriorized teflon arteriovenous fistula.

Management of Renal Failure

Dr. J. S. ROBSON was the moderator in a panel discussion on renal failure and its management. The members of the panel were Mr. DAVID BAND (Edinburgh), Dr. F. M. PARSONS (Leeds), and Dr. K. G. LOWE (Dundee).

Dr. LOWE outlined the history of the artificial kidney in acute renal failure. In Great Britain, after the second world war, the emphasis had been on conservative treatment, for reasons which included the hazard of infection during haemodialysis and lack of antibiotics, apart from penicillin. The undoubted success of the Hammersmith conservative regime in many patients delayed the development of haemodialysis in the treatment of traumatic anuria, which still caused a high mortality. Now, however, there was an adequate national haemodialysis service. In the many units there was an aggressive attitude towards further reduction of mortality by earlier "prophylactic" dialysis in acute renal failure, and towards lengthening the expectation of life by repeated dialysis in selected patients with chronic renal failure.

Dr. PARSONS described the principles of the artificial kidney, emphasizing that haemodialysis was now virtually free from complications. Renal disease requiring this treatment fell into three categories: acute reversible renal failure (tubular necrosis); acute glomerular disease; and chronic renal failure. In the second category, investigation, including renal biopsy, was often required to determine whether the disease was reversible or irreversible. The third category was subdivided into surgical and medical cases. In the surgical, dialysis might be required prior to operative relief of post-renal obstruction or to prepare a patient with chronic renal failure for operation on a lesion outside the urinary tract. In the medical group the place of dialysis was less clear: perhaps the main indications were very slow deterioration of renal function and sudden deterioration due to infection or gastro-intestinal upset.

Dr. Parsons subdivided his patients in whom dialysis for acute reversible renal failure, including acute glomerular disease, was indicated into mild cases (B.U.N. rising at less than 30 mg./100 ml. per day) and severe (B.U.N. rising at more than 30 mg./100 ml. per day). The mild group required dialysis only when clinical deterioration occurred —this usually being associated with a B.U.N. of 180–200 mg./100 ml. The severe group required dialysis even in the absence of clinical deterioration when the B.U.N. reached 120–150 mg./100 ml. With smaller machines than his at Leeds, the critical level of B.U.N. might be 100–110 mg./100 ml.

Dr. J. P. MERRILL (Boston, Mass), in the discussion, said it was essential for an artificial-kidney team to be skilled in conservative methods of treatment. Of 900 patients with acute renal failure admitted to his unit, 500 had been treated conservatively. He approved of earlier prophylactic dialysis, which had the important advantage of increasing the patient's resistance to infection.

Dr. A. C. KENNEDY (Glasgow) described a patient who had died apparently without cause after successful dialysis, and the panel agreed that, with the bigger machines especially, there was a risk of too efficient dialysis being fatal owing to sudden biochemical changes.

Mr. BAND, Dr. PARSONS, and Mr. ARTHUR JACOBS (Glasgow) discussed the problem of prostatic obstruction

with long-standing chronic uraemia. Catheterization was often effective, but dialysis rapidly improved the general condition and led to earlier prostatectomy; the risk of infection was diminished. Mr. Band warned against too early operation when the bladder was atonic. Dr. ROBSON introduced the topic of the mechanism of anuria and subsequent diuretic phase in acute renal failure. Was anuria the result of acidosis causing vasoconstriction? Dr. MERRILL thought that, despite a relatively normal renal blood flow, there was patchy ischaemia resulting in interstitial oedema which compressed the tubules; the diuretic phase began when the intratubular pressure overcame the increased interstitial pressure.

Nephrotic Syndrome

Dr. MARY K. MACDONALD (Edinburgh) spoke on the microscopy of the kidney. She presented the renal biopsy findings in 34 adult cases of proteinuria in which there was no clinically recognizable cause. On light microscopy a high incidence (6 cases) of normal glomerular histology was found; in each instance electron microscopy revealed abnormalities in the glomerulus consisting of patchy slight thickening of the capillary basement membrane and "smearing" of the foot-processes of the epithelial cells. These were beautifully illustrated by electron micrographs. In 8 cases features of membranous glomerulonephritis were found on light microscopy, and it was possible on electron microscopy to divide this group into two distinct types. In the first the changes in the basement membrane and epithelial cells were similar to those observed in the group with normal histology and differed only in severity. In the second there was gross irregularity in both the thickness and the structure of the basement membrane, and the surface projections of this membrane frequently interdigitated with smeared epithelium. In one case of postural proteinuria electron microscopy revealed very slight patchy thickening of the basement membrane and some of the epithelial-cell foot-processes were abnormally thick and rounded. The effect of steroid therapy was illustrated in a case with normal glomerular histology where clinical cure was associated with the resolution of the abnormalities in the fine structure of the glomerulus. A similar result was obtained in a patient with early membranous glomerulonephritis, but it was followed by relapse when steroids were withdrawn. The resumption of steroid therapy was again associated with clinical cure and the disappearance of the basement membrane and epithelial cell abnormalities.

Dr. G. C. ARNEIL (Glasgow) discussed steroid therapy of the nephrotic syndrome in childhood. His data, collected over a period of 28 years, showed a marked improvement in prognosis after the introduction of steroid therapy. This could not be attributed to the advances made in the treatment of infection. He had found prednisolone the most satisfactory steroid and he recommended large doses initially. Side-effects of treatment included Cushingoid features and arrested body growth. Additional measures in treatment were a low-sodium, isocaloric diet, chlorothiazide in steroid-resistant cases, and antibiotics when infection occurred. In successful steroid therapy the diuresis occurred before an increase in the serum albumin level could be detected, and it had been found that the onset of the diuresis and the reduction in proteinuria occurred simultaneously. A diuresis induced by chlorothiazide was not associated with a decrease in proteinuria.

Dr. E. LOVELL BECKER (New York) briefly reviewed immune mechanisms in the nephrotic syndrome. Renal biopsy material from patients with membranous glomerulonephritis, demonstrated by fluorescein microscopy, showed the deposition of gamma-globulin in the region of the basement membrane. Although there was much evidence to support the existence of immune mechanisms in both the membranous and the proliferative forms of glomerulonephritis, Dr. Becker emphasized that these were not necessarily the initiating factors in the disease. It was conceivable that antibodies or "acute phase substance" might arise secondary to initial tissue damage without being pathogenic, or if they were pathogenic they might merely be exacerbating an already existing disease process.

In the discussion on these papers, Dr. Becker said that his group had formed the impression that membranous glomerulonephritis in which the electron-microscopic features resembled those found in cases with normal histology (on light microscopy) probably represented a more advanced stage of the same disease process, and wondered whether Dr. MacDonald agreed with this view. Dr. MACDONALD replied that these appearances had been most frequently observed in children, and on morphological grounds she agreed that the finding of the "child's lesion" in membranous glomerulonephritis probably represented a more severe or advanced form of the group which failed to show any abnormality on light microscopy.

Renal Transplantation

Dr. J. P. MERRILL gave the second Sydney Watson Smith lecture, on the subject of renal transplantation. He first discussed some general problems of tissue grafting. A piece of skin grafted from person A on to person B began to be rejected after 5 days. Antigens from the graft reached the regional lymph nodes and the sensitized lymphocytes assumed destructive properties. A second skin graft was rejected even more rapidly (accelerated reaction). The accelerated reaction was not organ-specific—an important point, since a kidney would be rejected more rapidly as a result of previous skin grafting. In an animal made hypersensitive by a series of skin grafts, the last rejected graft showed remarkably little histological change (white graft reaction). Instead there was perivascular cellular infiltration and thrombosis of the host's blood-vessels near the graft, leading to ischaemic rejection. This suggested that at least part of the local rejection mechanism took place in the host's tissues.

Dr. Merrill then turned to the more specific problem of renal transplantation. In the dog a transplanted kidney ceased to function after 5 days. The most significant histological change in the rejected kidney was infiltration with round cells. The position in humans was different and a little more favourable. In chronically uraemic humans rejection was slower and the cellular infiltration was polymorph in nature. The difference was, no doubt, partly a matter of species, but the retarding influence of chronic uraemia was also important. Dr. Merrill related his own experience of 23 human transplants (*not* in identical twins). In 3 the transplanted kidney survived long enough to be of some use, and in 1 of these 3 there was reasonably good function of the kidney after 5½ months. In identical twins there was, of course, no immunological problem. Sixteen identical-twin transplants had now been done throughout the world —14 in the U.S.A. (including 12 in Dr. Merrill's own unit at Boston), 1 in Canada, and 1 in Edinburgh. In such cases, apart from the difficulties of surgical technique, there was a danger that the transplanted kidney might develop the same disease as the recipient's original kidneys. This applied particularly to glomerulonephritis, but probably not to pyelonephritis. The risk might be lessened by preliminary bilateral nephrectomy, thus removing a possible antigenic stimulus to the development of glomerulonephritis. In one such patient, who was without kidneys for 12 days, Dr. Merrill had made an interesting incidental observation that the blood pressure remained normal. This was against the theory that there was a renoprival type of hypertension.

Dr. Merrill then discussed the problem of attempting to produce immunological tolerance in a person who had no identical twin. One method was to destroy the haemopoietic system by *x*-irradiation followed by marrow transfusion. Unfortunately in the human transfused marrow failed to survive for more than a few months, and, in addition, being immunologically competent, produced a graft-versus-host reaction, which might be fatal. It was possible, however, to limit *x*-irradiation to make the haemopoietic system "sick" and hence, in a sense, immunologically immature. Further

limited *x*-irradiation could be given at intervals after transplantation, possibly combined with steroid therapy. Radiomimetic agents, such as 6-mercaptopurine, could be used instead of or as a supplement to *x*-irradiation. Dr. Merrill pointed out that the place of these potentially dangerous procedures was not yet clearly defined and he did not want to paint a rosy picture.

In looking to the future of renal transplantation, Dr. Merrill emphasized that, immunologically, the kidney was a relatively favoured organ. It did not produce a graft-versus-host reaction. Furthermore, renal transplantation was equivalent to giving a large dose of antigen intravenously—a method known to facilitate the establishment of tolerance experimentally. Possible developments lay in new techniques of "matching" tissues, selective injury to lymphopoietic tissue without destruction of bone marrow, and use of anti-serotonin agents to prevent vascular rejection mechanisms.

Discussion on Renal Transplantation

After his lecture Dr. J. P. Merrill was the moderator of a panel discussion on renal transplantation, in which the members of the panel were Dr. J. R. Anderson (Glasgow), Professor R. McWhirter (Edinburgh), Professor M. F. A. Woodruff (Edinburgh), and Dr. J. S. Robson (Edinburgh).

Dr. ANDERSON referred to the basic problems in immunology fundamental to renal transplantation. The immune response could be suppressed by modifying (*a*) the graft, or (*b*) the host. In the case of the kidney, the closer the donor and recipient were genetically, the weaker would be the immune response. In closely related pairs the number of antigens capable of producing immune response was very small, and in similar twins, antigenically alike, the immune response was absent. The graft, therefore, took successfully.

Methods of producing tolerance were (1) conditioning the foetus, too immature to show immune response, by a graft (a suspension of cells). When the foetus grew to maturity it would have developed specific tolerance to the donor of the original graft, and could accept further grafts successfully. (2) In the adult the immune reaction could be suppressed by irradiation, as had been shown by Merrill and his colleagues, and also by Küss in Paris. When whole-body irradiation had been given it was possible that the graft itself might then react against the host. Dr. Anderson concluded by referring to the possibility that the foetus and the mother might develop mutual partial tolerance during gestation.

Dr. MERRILL said that renal transplants between parents and children had been disappointing, but the possibility that infants with icterus neonatorum, who had received large transfusions, might develop tolerance to a specific blood donor should be explored. He referred to a renal homograft which had already survived for more than 18 months in a case of non-identical twins. Tolerance was produced by repeated small doses of whole-body irradiation, and he considered that this technique could perhaps be combined with the use of 6-mercaptopurine.

Professor WOODRUFF said that, in his experience, compatibility of blood groups was not a sufficient guarantee of success in homotransplantation. The homograft problem had been solved in the laboratory, where a high degree of tolerance to homotransplants could be induced in a mammal by the post-natal injection of donor cells. Nature occasionally produced this result in non-identical (dizygotic) twins who, on account of admixture of their placental circulations, became erythrocyte chimeras. Such twin chimeras were tolerant of each other's tissues and could interchange skin grafts.

Professor MCWHIRTER, referring to whole-body irradiation, said that a sublethal dose given to a patient to condition him to receive a graft was difficult to estimate. Under 400 r was perhaps the safest, and with supervoltage radiation the dose could be reduced. The risk of leukaemia, which was real and was also present with radiomimetic agents, was well justified.

Dr. ROBSON then spoke of the problem of infection in cases of renal transplantation. He firmly believed that infection in the recipient should be treated when it arose, and not before. The policy of "no prophylactic antibiotics" should be emphatically imposed. Dr. MERRILL agreed with that, but prophylactic antibiotics should be given when infection existed in the recipient.

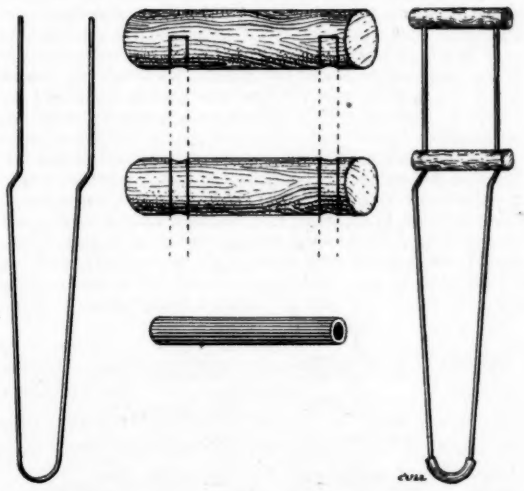
Professor WOODRUFF considered that the graft-recipient reaction could be limited by broad-spectrum antibiotics, and Dr. MERRILL agreed that some of the effects of "secondary disease" could be due to infection. Professor WOODRUFF also stressed the point that micro-methods of blood analysis to minimize the quantity of blood taken from the patient were desirable. Dr. MERRILL said that such methods were being developed successfully.

New Appliances

A SIMPLE CRUTCH

Mr. DENIS BURKITT, specialist surgeon, Uganda Medical Services, writes: In underdeveloped countries many people are deprived of effective medical treatment owing to limited hospital accommodation. Yet patients with leg injuries are often retained longer than necessary for lack of a suitable crutch to render them ambulant.

Hospital authorities are naturally reluctant to issue elaborate adjustable crutches which might not be recovered, and the commonly used "T" model is useless for weight-bearing. Moreover, there are many sedentary cripples who, with a means of locomotion, might be converted into ambulant workers.



A search has been made for a crutch pattern combining effectiveness and comfort with simplicity and economy. The pattern illustrated appears to meet these requirements. The only materials required are: (1) iron rods as used by any building contractor (⅜ in. (1 cm.) diameter for adults, ¼ in. (0.6 cm.) diameter for children); (2) a broom handle; and (3) rubber tubing (that used for garden hose is very satisfactory); its life can be considerably lengthened by using a large piece of tubing which can be moved along the iron rod as the weight-bearing area becomes worn. The hand-grip is placed at one-third of the length of the crutch from the upper end.

A crutch can be shortened by cutting a piece from the ends of the iron rods, and the hand-grip can be raised by threading a short length of piping on to each limb before placing the hand-grip. The rubber tube, when worn, can

be easily replaced after removing the two cross-bars. The "U" bottom is thought to be better than the conventional peg end.

Such a crutch can be made at any hospital in a matter of minutes with a minimum of equipment. This pattern has been adopted by the Uganda Medical Service and the Mulago Round Table Polio Clinic. The diagram was drawn by Mr. Peter Gull.

A SET OF GUIDE AND BOUGIES TO FACILITATE INSERTION OF MOUSSEAU–BARBIN TUBES

Mr. F. T. CROSSLING, senior registrar, Stobhill General Hospital, Glasgow, writes: It is an unfortunate fact that many cases of carcinoma of the oesophagus, particularly where the mid or upper third is involved, are beyond surgical cure when the patient is first seen.[1,2] When one is confronted with this situation on clinical investigation or at operation, it is still essential to attempt some form of palliation to enable the patient to swallow, and intubation of some kind is often the best method.[3,4]

The original Souttar tube has the disadvantage that food becomes enmeshed in its wall and causes blockage. Also it may readily be displaced and passed beyond the stricture into the stomach. However, there are now a number of modified forms made of plastic materials.[5,6] From considerable experience in the use of the Mousseau–Barbin tube we find that food is less likely to adhere to a plastic tube, and that the large flange prevents displacement. The Mousseau–Barbin type has been justifiably popular despite possible trouble with pressure necrosis at the funnel end of the tube, but in our hands preliminary dilatation with bougies has been a greater problem.[7] One can only too easily transgress the oedematous and infiltrated oesophageal wall even when great care is taken, although it is a remarkable fact that, despite the presence of a traumatic rupture of the oesophagus due to bougienage, a successfully passed Mousseau–Barbin tube will seal the gap and continue to function satisfactorily without the development of mediastinitis.

The eventual passage of one bougie as confirmed by a finger in the stomach is no guarantee that subsequent larger bougies will follow the same route. Therefore, in order to facilitate both bougienage and insertion of the tube, a set of gum-elastic oesophageal bougies has been devised which can be linked together by a simple screw attachment to form a continuous length. The set, which consists of five bougies, sizes 13, 15, 17, 19, and 21 (English gauge) (Fig. 1), gives

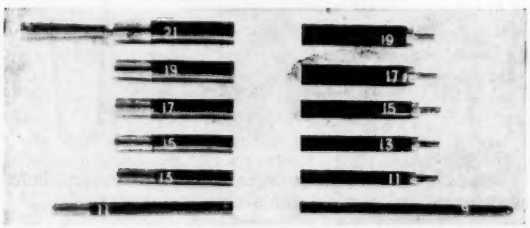


FIG. 1

sufficient dilatation to permit easy insertion of a size 10 or 12 Mousseau–Barbin tube. The guide bougie, which is of gauge 11, is 70 cm. long (15 cm. longer than the standard gum-elastic bougie) (Fig. 2). It can thus be passed right into the stomach while leaving sufficient length projecting from the mouth to facilitate attachment of subsequent bougies. As the guide bougie is pulled out of the gastrotomy one bougie after another is attached and pulled through until enough dilatation is achieved. The cone-shaped adapter, which can be screwed into the proximal end of any of the bougies, is then attached, and to this the tip of the Mousseau–Barbin tube is secured by suture and is pulled through (see Fig. 2). The conical shape of the adapter allows the fixation suture to be recessed behind the last bougie and so prevents further trauma to the friable oesophageal wall.

A Mousseau–Barbin "stylet" is available, and this certainly facilitates introduction but does not allow of any

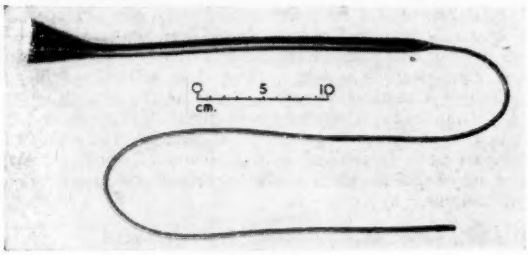


FIG. 2

gradual dilatation of the malignant stricture. We feel that the method described is safer. It has now been successfully employed in a number of cases in Stobhill Hospital, Glasgow.

I am grateful to Mr. J. Hutchison for permission to publish this report.

The equipment was manufactured by Charles F. Thackray Ltd., and I am indebted to their representative, Mr. Bury, for his close co-operation.

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Nova et Vetera

MEMOIRS OF F.R.S.'s

With commendable promptitude a sixth volume in this informative series has appeared.[1] It contains memoirs with full bibliographies of 17 Fellows who died from 1958 to 1960. They comprise two botanists; three zoologists (including two entomologists); five chemists; five physicists (including one metallurgist); one pharmacologist; and a millionaire philanthropist. Seven of these were foreigners—two Frenchmen, two Germans, one Austrian, one Dane, and one American. The memoirs are written with personal knowledge of the deceased Fellows; and for the most part by those who have worked with them.

Place aux dames, and the volume opens with an account of Mrs. Agnes Arber, the botanist, an authority on the anatomy and morphology of monocotyledonous plants. In her later years she wrote on philosophy. She was the third woman to be elected F.R.S. Much of the research work of Fellows recorded here was in different branches of pure and applied science, but some of it has a direct bearing on medicine—for example, the investigations of the German physicist Max von Laue on *x*-ray diffraction in which he succeeded where

[1] *Biographical Memoirs of Fellows of the Royal Society*. Volume 6. (Pp. 295; illustrated. 30s.) London: The Royal Society, Burlington House, W.1. 1960.

Röntgen had failed. There is also the munificent work of J. D. Rockefeller, jun., in carrying out his father's aim to endow and support medical research throughout the world. M. Joliot's work on radium and atomic energy is well described, while the conveyance of heavy water from Norway to France and later from France to England during the last war has all the atmosphere of an adventure story. The life and work of Bruno Mendel, M.D.Berlin, the pharmacologist, is narrated by W. S. Feldberg. Mendel's best-known work, done at Toronto, is that on cholinesterases, which is of importance for the theory of chemical transmission of nerve impulses by acetylcholine. Indeed, the whole volume chronicles the steady progress of scientific research in many fields of endeavour.

ARTHUR S. MACNALTY.

150th ANNIVERSARY OF THE MOORFIELDS SCHOOL OF OPHTHALMOLOGY

The founders of Moorfields Eye Hospital in 1805 had especially in mind the need for teaching facilities in the specialty. As a result within a few years the School was officially started and its 150th anniversary is now being celebrated.

In addition to the early clinical instruction, set classes were being held by about 1820, even the honorary chaplain of the hospital doing his share with physicians and surgeons by giving the optics lectures. Within twenty years over 1,000 doctors had attended the school, and scattered again to all parts of the world, a pattern which has been maintained to the present day.

Early students soon founded eye units not only in Britain but in New York and Boston and under the aegis of the East India Company in Madras, Bombay, and Calcutta. These units all flourish to-day, and many others, especially in the Commonwealth countries, have been largely staffed over the years by men and women trained at Moorfields.

The invention of the ophthalmoscope, the discovery of anaesthesia, and the rapid and exciting advance in scientific medicine from the middle of the century onwards enormously widened the scope of ophthalmology and disclosed its many associations with general disease. Sir William Bowman, first a general surgeon and physiologist, was appointed dean in 1847, and his name and those of other surgeons like John Dalrymple, Jonathan Hutchinson, and Edward Nettleship are of course well known outside ophthalmology. By encouraging clinical assistants Moorfields profited and widened its teaching effort. Among the keenest clinical assistants were Hughlings Jackson—from whom stems the close link with Queen Square—and Osler, who intended originally to practise ophthalmology, changing to general medicine only when he learned that a fellow Canadian from Moorfields had forestalled him at home. The original articles from staff and assistants published in the early clinico-pathological hospital reports make delightful reading to-day, and show how acute and well-founded were their observations and how high their skill with few of the scientific aids now available.

The School flourished till the first world war, but the lean years this brought and the establishment of a new diploma in the specialty called for a considerable expansion of the set lecture course. Lack of space and money

(*Continued at foot of next column*)

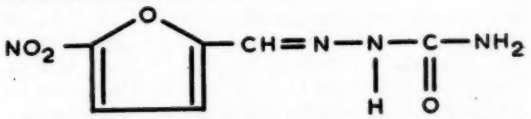
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

Nitrofurazone

"Furacin" (Smith Kline and French).

Chemistry.—This is a nitrofuran compound with the chemical name 5-nitro-2-furaldehyde semicarbazone and the following structural formula:



It is a yellow crystalline compound, poorly soluble in water but more soluble in alcohol or acetone. It is stable and does not lose activity on autoclaving.

Antibacterial Action.—Nitrofurazone is active against a wide range of bacteria, including *Staphylococcus aureus, Streptococcus pyogenes* and many Gram-negative bacilli, but less active against *Pseudomonas pyocyanea.* A limited degree of resistance can be induced *in vitro,* but resistance is said not to emerge in the bacteria of patients treated with the drug. Its action depends on a prolongation of the lag phase of bacterial development, and there seems to be no effect on the rate of growth of actively multiplying bacteria. The antibacterial action is reported to be somewhat reduced in the presence of blood or serum.

Therapy.—Nitrofurazone is suitable for local application only. It is available in the form of an ointment (0.2% with polyethylene glycols) or as a solution (0.2% with polyethylene glycols, cetomacrogol, and water). When applied to burns, the ointment has been found to have some prophylactic action against *Str. pyogenes* and to improve the "take" of skin grafts, but the effect was smaller than it was when a broad-spectrum antibiotic (chloramphenicol) was similarly tested. There are reports of benefit in the treatment of infective dermatitis and of a variety of open wounds, and the substance is also said to have been of value in the treatment of otitis media and externa and of urethritis.

Side-effects.—Sensitivity reactions (papular or macular rashes, which usually disappear soon after treatment is stopped) have been found in about 3–4% of patients treated, and especially in those with extensive raw areas to which the drug has been applied for a week or longer. There appears to be no interference with healing of wounds and no irritation of tissues.

N.H.S. Basic Price.—Soluble ointment, 1 oz. for 2s. 8d.: solution, 4 fl. oz. for 6s. 6d.

(*Continued from preceding column*)

without university recognition and aid meant many difficulties and frustrations, but persistent effort by successive deans and the foundation of the British Postgraduate Medical School kept hopes high. The second world war deferred these hopes and again severely restricted the School's work, but as the result of much planning the three eye hospitals, familiarly known as Moorfields, Royal Westminster, and Central, were amalgamated in 1947. All the clinical work was retained in the first two, and the building of the last-named was adapted to become the Institute of Ophthalmology; this Institute within the Postgraduate Federation of the University achieves the ideal for which before 1930 Parsons, Lister, and others had so long sought. A long line of teachers, physicians, and surgeons of the hospital, including among them several Presidents of the Royal College of Surgeons and Fellows of the Royal Society, will be remembered in the present celebrations.

R. C. DAVENPORT.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Educational Facilities for Overseas Graduates

SIR,—Successive issues of the *Journal* have testified to the increasing awareness of many in this country and abroad that more could and should be done for medicine in the Commonwealth. Sir Douglas Robb in his Presidential Address to the British Medical Association (February 11, p. 376) drew attention to the way in which different countries of the Commonwealth could help one another. At the Commonwealth Conference in Auckland a Commonwealth Medical Association was proposed (February 11, p. 420). Professor Kenneth Hill has made a plea (January 14, p. 117) for secondment of staff from British universities to those overseas, and Professor Ian Aird (February 18, p. 499) has proposed that university budgets for the next quinquennium should provide for posts jointly between British and African universities, thus enabling men to spend five years abroad and subsequently to return to a post in this country with security of tenure.

These are altogether admirable suggestions, but I do not think they go far enough. The purpose of this letter is to suggest another way in which we could help the emergent nations, and incidentally put our own house in better order.

My visits to Commonwealth countries of Africa and Asia and the Caribbean as well as to foreign countries in the Middle East leave me in no doubt that there is a great urge in these countries to improve university standards in general, and particularly in science, technology, agriculture, and medicine. These countries, whether inside or outside the Commonwealth, need not only teachers in their schools and universities, to which the above-mentioned proposals would contribute; they need facilities for their graduates to complete their training abroad. Only those who have visited Eastern countries which are now independent can realize the urgency and magnitude of this need. In a recent visit to the Middle East the university teachers in medicine, and the sciences basic to it, explained to me how disturbed they were at the difficulty of getting their best students places in our universities to read for D.Phil. degrees, and places for their best clinical students in the postgraduate medical schools in London. If we cannot provide these facilities, the students will go elsewhere. At the present time the countries of eastern Europe and the West German Republic are seeking to attract as many as they can. We have, however, an overwhelming natural advantage in that postgraduate students coming here do not as a rule have to receive instruction through the medium of a language with which they are unfamiliar.

Some idea of the present size of this problem is given in the report of Sir Robert Platt's Working Party in your *Supplement* (March 25), which shows how dependent our non-teaching hospitals are for their junior staff on doctors from overseas, the proportions in England ranging from 32% in Wessex to 51% in the Newcastle and Sheffield regions. Most of these come from the relatively under-developed countries, and most come with the prime object of furthering their education. The very size of the problem means that, whatever we do in the teaching hospitals for these visitors, most will have to be accommodated in non-teaching hospitals.

It was clearly the intention of the Health Service, when it was arranged by regions centred on universities, each with an officer responsible for postgraduate education, that something should be done to organize postgraduate education within this pattern. If, as everyone agrees, junior hospital posts are at least partly educational in function, should some attention not be given to what facilities are needed for this education and how these facilities can best and most economically be provided? In the non-teaching hospitals I know, up and down England, I fear that these facilities are not provided; further, very little thought has been given to what they should be. Except in our teaching hospitals we are woefully behind the United States in facilities and training programmes for postgraduates. Quite apart from the needs of overseas visitors, it is high time for a survey of what can and should be done to improve postgraduate education, particularly outside the teaching hospitals.

No one who is closely familiar with undergraduate education, and indeed with every aspect of learning in our teaching hospitals, can doubt that an almost miraculous change has been wrought in the last 20 years, and that the greatest single factor has been the report of the Interdepartmental (Goodenough) Committee on Medical Schools (in 1944) and its implementation. Is it not time that another interdepartmental committee should be set up to consider the needs of postgraduate medical education in this country and the best way to meet these needs? And since this is one of the services that are needed and wanted by the under-developed nations within the Commonwealth and outside it, might this committee also consider how best this country could help the advancement of medicine in these countries — for example, by supplying them with teachers? Though I would hope that sensible suggestions for supplying teachers would be tried at least as pilot schemes without delay. As before, the Ministry of Health and Department of Health for Scotland would be chiefly involved, but the Ministries responsible for the universities, and for Foreign, Commonwealth, and Colonial affairs, would presumably not be disinterested.

In medicine, at least, the problem will not wait, and if we in Britain do not supply the needs of the under-developed world, others will. Moreover, the Health Service is now twelve years old and is beginning to settle down. The basic facilities for the development of postgraduate medical education exist in the regional arrangement of the Health Service. The time is ripe for the universities to use them. But it needs a little thought and discussion to use them rightly.—I am, etc.,

Oxford. G. W. PICKERING.

National Epidemiology

SIR,—A central register of personal health records would be extremely valuable, if not indispensable, for determining some of the facts required for study of the causes, course, and response to treatment of many diseases, among which mental disorders are conspicuous. The rapid extension of psychiatric services to general hospitals, and the trend towards dealing with

patients in the community rather than in mental hospitals, has made it more difficult to collect comprehensive data. The increased frequency of readmissions has strengthened the case for having systematic information about persons, rather than about events such as admissions and discharges.

The Registrar-General's recent cohort study of all patients admitted for the first time to mental hospitals demonstrated that such information is of the greatest value for epidemiological and kindred research, provided there is some means of discovering the subsequent medical history of the people concerned. For such a purpose a central register like that suggested in the letter from Dr. E. D. Acheson, Dr. S. C. Truelove, and Professor L. J. Witts (March 4, p. 668) would be essential.—I am, etc.,

The Maudsley Hospital, London S.E.5. AUBREY LEWIS.

SIR,—The letter from Dr. E. D. Acheson, Dr. S. C. Truelove, and Professor L. J. Witts (March 4, p. 668) was so comprehensive and so compelling that there appeared to be no need for anyone else to elaborate it. It would, however, be unfortunate if lack of correspondence were to imply lack of support, and, in view of Dr. M. A. Heasman's request (March 18, p. 821), I would like to express my enthusiasm for the proposal. It is not difficult to explain this reaction, because so much of the work with which I have recently been concerned would have been transformed if each patient had always been given the same case number at every hospital, and if the same number could also be connected with his birth and death certificates. It is not only that the work of, say, following 15,000 patients who had been irradiated for spondylitis would have been easier; it would also have been better. We should, for example, have been less likely to miss identifying the patient treated at two or more hospitals and less likely to underestimate the dosage by omitting treatments. In other cases, the ability to link past hospital admissions creates the possibility of carrying out investigations which would otherwise be impracticable. With the aid of a central hospital register it should be possible to decide whether or not exposure to the small amounts of radiation involved in diagnostic radiography is leukaemogenic. Dr. Acheson and his colleagues referred to the enormous potentialities of the register in the genetic field; twin studies are an obvious example. Within quite a short period the register could provide conclusive evidence on the extent to which hereditary factors may contribute to disease.

It is, of course, realized that the cost of such a scheme would be substantial, and there are important problems concerning the confidentiality of medical records to be solved. I doubt, however, whether the practical details would be so great as have sometimes been thought. The great majority of patients who attend hospital have attended the same hospital previously, and their N.H.S. numbers will already have been linked with their names in the hospital records. Many others would bring their personal medical cards with them if encouraged to do so; and it might not be impossible for some practitioners to record the number on letters requesting a hospital opinion. If all else failed the hospital records department should be able to obtain the number without great difficulty from the local executive council. Clearly, there will be need to experiment, and it would be premature to decide upon a national scheme without a realistic estimate of the cost and of the practical difficulties. Dr. Acheson, Dr. Truelove, and Professor Witts suggest that a pilot study might first be carried out on a regional basis. This seems a most excellent suggestion, and where could it be done better than in Oxford?—I am, etc.,

RICHARD DOLL.

Statistical Research Unit, London School of Hygiene and Tropical Medicine, London W.C.1.

Micturition Syncope

SIR,—I fear that neither your annotator (March 18, p. 805) nor the American writers[1 2] on this subject are beer drinkers, and once more clinical speculators have backed the wrong mechanism. This circulatory disturbance is within the personal experience of many of us. There is no question of performing the Valsalva manœuvre. Half asleep, stumbling, hot, the victim stands to empty a very full, low-pressure bladder. He breathes easily while he does so and does not strain. At about ½ to ¾ evacuation the heart rate accelerates, the pulse pressure and mean arterial pressure decrease, and the subject, still breathing easily, is often conscious of the beating of his heart. At this point syncope or more usually dizziness occurs, and commonly the subject supports himself with one hand on the wall. While there are other situations where the Valsalva manœuvre will cause syncope on getting out of bed, this is not one of them.

It is more difficult to be constructive, as no measurements have yet been made. I suspect that reflex dilatation of the peripheral venous system occurs, and it is tempting to see some connexion with the startling hypertension which can be produced in paraplegics by the opposite manœuvre of bladder distension. I would suggest that the sex difference is not due to the short wide urethra of the female preventing the need to strain, but to the difference in posture of the two sexes while micturating and, of course, to the quantity of beer each is prepared to consume.—I am, etc.,

E. P. SHARPEY-SCHAFER.

Department of Medicine, St. Thomas's Hospital Medical School, London S.E.1.

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SIR,—Your annotation (March 18, p. 805) states that micturition syncope invariably occurs in healthy males.

A patient of mine aged 64 years, suffering from pulmonary tuberculosis, rheumatoid arthritis, and duodenal ulcer, collapsed in the toilet in January of this year. He stated that he had started to micturate, hesitated, and then fell down unconscious. On three further occasions in the next 24 hours he again became unconscious shortly after starting to micturate. He was collapsed and pale, but his blood-pressure remained within normal limits, as it had been on admission. He subsequently admitted to a history of nausea and indigestion and there was evidence of gastric dilatation confirmed later on *x*-ray.

It would appear, therefore, that micturition syncope is not confined to *healthy* males as stated.—I am, etc.,

A. E. R. CAMPBELL.

Bellefield Sanatorium, Lanark.

Imipramine in Depression

SIR,—I have just seen the paper by Drs. L. G. Kiloh and J. R. B. Ball on imipramine ("tofranil") in depression (January 21, p. 168). I would like to report a side-effect which appears uncommon, as they do not mention it.

Out of five patients who are currently on maintenance treatment with imipramine, two have complained of palpitations, and have been found to have a pulse rate between 120 and 140 per minute. One developed tachycardia after she had been taking 150 mg. daily for about two months; the other patient had been given 75 mg. daily by mouth and 75 mg. daily by injection for only a few days. In both cases the pulse slowed when the dose was reduced to 100 mg. a day. Both patients later relapsed when the dose was reduced further; in one, return to 150 mg. daily has led to return of the tachycardia.

May I add, without at this stage giving further details, what a boon this drug has proved in general practice?—I am, etc.,

Waroona, West Australia. PAUL MESTITZ.

Phenazocine and Respiratory Depression

SIR,—I read with interest the letter from Dr. Ronald Shaw (March 18, p. 825) on the subject of phenazocine ("narphen") and respiratory depression. Like Dr. Shaw, I also have made some investigations into the effects of this drug upon respiration in anaesthetized patients, assessing tidal volume and minute volume by means of a dry gas meter. I found its effects to be very variable and unpredictable from one patient to another, as the following typical case reports illustrate.

Case 1.—A fit young man of 18: for wiring of fractured patella. Light anaesthesia of thiopentone, nitrous oxide, and oxygen with halothane 1% from a calibrated vaporizer. Tidal volume (T.V.) at commencement was 290–320 ml., respiratory rate 35/minute. Phenazocine 0.5 mg. intravenously resulted, after 45 seconds, in a fall of T.V. to 70–100 ml., with a rate of 18/minute. This gradually increased to 280–300 ml. after six minutes, with a rate of 22/minute. Phenazocine 0.5 mg. was then repeated, resulting almost immediately in respiratory arrest for 6½ minutes, necessitating controlled respiration. There was a gradual recovery over the next 20 minutes, with T.V. at first in the range 100–250 ml. and irregular respiratory rhythm. After 21 minutes T.V. was 430–440 ml. and the rate 16/minute.

Case 2.—A rather frail woman aged 53: for transnasal hypophysectomy for carcinoma of the breast. Anaesthesia: hydroxydione 1.0 g., suxamethonium, nitrous oxide, oxygen, and halothane 1.0%. Initial T.V. was 220 ml., rate 32/minute. Phenazocine 0.5 mg. intravenously produced no change in T.V. or respiratory rate over a period of 10 minutes. Three further increments of 0.5 mg. were given at ten-minute intervals, making a total of 2.0 mg. intravenously. These produced a gradual fall in respiratory rate to 18/minute, but T.V. rose steadily to 340–350 ml.

Case 3.—A fit young man of 25: for inguinal herniorrhaphy. Anaesthesia: thiopentone, nitrous oxide, oxygen, and halothane 2.0%. Initial T.V. 350 ml., respiratory rate 30/minute. Phenazocine 1.0 mg. intravenously led to respiratory arrest in 30 seconds. This persisted for 18 minutes, although the halothane vaporizer was turned off. Respirations reappeared at 4/minute when the skin sutures were being inserted. Levallorphan 1.0 mg. intravenously reversed the respiratory depression completely and the patient awoke immediately.

It is clear from the above case reports that intravenous phenazocine may exert an extremely powerful and persistent respiratory depressant effect, reversible by levallorphan but not readily predictable.

The literature distributed with the drug states that it may be given in obstetrics in doses of 2.0 mg. intramuscularly or intravenously as an initial dose, followed by 1.0 or 2.0 mg. as required. This is clearly an extremely dangerous and ill-advised recommendation, and I have no doubt that the intravenous use of phenazocine should be restricted to the operating theatre. There it may find a small place in the anaesthetist's armamentarium — e.g., the control of spasmodic diaphragmatic contraction in gastric and upper abdominal surgery, or in controlled respiration along the lines suggested by Colemen *et al.*[1]—I am, etc.,

Selly Oak Hospital, Birmingham 29. A. VIVIAN JENKINS.

REFERENCE

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Thrombophlebitis Migrans

SIR,—Diagnoses are labels given to patients' diseases and should help and not hinder us in understanding the aetiology, clinical course, and prognosis of the disorder. Too often descriptive terms or syndromes become accepted into current use and official nomenclatures as disease entities with the result that underlying primary diseases tend to be forgotten. One such title is Reiter's disease. Thrombophlebitis migrans is another example. This was the title of Dr. P. M. S. Gillam's interesting memorandum (March 11, p. 721), and it has a curious history.

Jadioux[1] described a case of "la phlébite spontanée," the earliest in the *Surgeon-General's Index*. Jadioux's patient was a healthy man, aged 20, who suddenly developed a thrombosis of his left external iliac vein and later oedema of the whole limb. Such phlebitis was soon found to occur in patients with general disease, so that twenty years later Trousseau[2] would remind his students: "Vous vous rappelez que nous avons étudié l'œdème blanc douloureux, non seulement chez les femmes récemment accouchées, mais plus souvent encore chez les malades des deux sexes affectés de phtisie pulmonaire ou de tumeurs cancéreuses profondes. . . . L'expérience clinique m'a démontré toute la valeur sémiotique de la phlegmatia dans les cachexies cancéreuses en particulier."

Sir James Paget[3] gave a clinical description of the disease to which little could be added to-day. After excluding those cases of phlebitis associated with trauma, exhaustion, extension of inflammation (from ulcers, morbid growths, or gangrenous or acutely inflamed parts), rheumatic, pyaemial or post-febrile, puerperal, and varicose, he was still left with "gouty phlebitis." This type of phlebitis might occur during acute gout, but also "with little or no evident provocation in those persons of marked gouty constitution, or with gouty inheritance." He describes the lesion vividly: "The inflamed portions of the vein usually feel hard or very firm: they are painful, aching and very tender to the touch; such pain, indeed, often precedes the clearer signs of the phlebitis; and not rarely begins suddenly."

Clinicians of the nineteenth century were fully conversant with the syndrome of primary phlebitis, and were content to describe it as idiopathic[4] or attribute it to a thunderstorm.[5] In this century the migratory nature of the lesion has been emphasized, especially by the use of the adjective *migrans*. Thus *wandernde phlebitis* was described in a syphilitic,[6] *phlebitis migrans (non syphilitica)* in a consumptive,[7] and migratory thrombophlebitis in patients with thromboangiitis obliterans.[8] Universal causes such as focal sepsis,[9] stress,[10] allergy,[11] toxins, and subacute venous septicaemia have been propounded. Local forms of the disease have even been given separate titles (e.g., Mondor's disease).[12] "Idiopathic

recurrent thrombophlebitis" was first used by Briggs[13] when he admitted ignorance of the nature of the disease, though he hoped "that we may be able eventually to refer these apparently mysterious cases to a variety of different causes."

Thrombophlebitis migrans is, as Ryle[9] said, an admirably descriptive name of a particular sign-complex. However, it is merely a descriptive term, and is not a precise diagnosis, since such recurrent thrombophlebitis may occur secondary to systemic or local disease, as well as primarily, for no discoverable cause. I have pleaded[14] elsewhere for the abandonment of this term as a diagnosis and for its replacement by idiopathic recurrent thrombophlebitis (if no primary disease is discovered) or secondary recurrent thrombophlebitis, where the underlying disease has been found.—I am, etc.,

Institute of Clinical Research, The Middlesex Hospital Medical School, London W.1. J. H. BARON.

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Reiter's Disease

SIR,—Dr. J. H. Baron (February 11, p. 426), commenting on the interesting article by Drs. J. K. Oates and R. M. Mason (December 24, 1960, p. 1878), suggests that it would be preferable to talk of Reiter's syndrome rather than Reiter's disease, so that the patient's condition is recognized as a complication of the primary disease (e.g., non-specific urethritis, bacillary dysentery, or ulcerative colitis). It is not possible, however, to accept this view for the following reasons.

(1) In non-specific urethritis following sexual exposure, although smears are abacterial and culture sterile, an *infective organism* must be postulated as the aetiological factor.

(2) The urethritis that may follow various dysenteric conditions is indistinguishable both clinically and in laboratory findings from that in (1) above, as again smears are abacterial and cultures always negative. Furthermore, in bacillary dysentery where the responsible organism is known (i.e., Shiga, Flexner, etc.) these organisms are never recoverable from smears and cultures of the urethral discharge.

It appears to me from these facts that one must conclude that the organism present in the female genital tract in cases of Group 1 (above) must be present in the bowel in those of Group 2, and that, owing to the pathological condition of the bowel wall, they find their way into the circulation. During elimination by way of the genital tract they give rise to urethritis (cf. *B. coli* infections of the genital tract). It further appears but a reasonable step to consider that the other features of Reiter's disease—i.e., arthritis, skin and eye lesions—arise from the same organism.

Reiter's disease therefore, if by this we mean urethritis, arthritis, skin and eye lesions (or any combination of these), appears to be correctly named on aetiological grounds. It appears to arise from an as yet unidentified organism (or group), and this organism is present in the female genital tract in cases following sexual exposure and within the bowel in cases following dysenteric upsets. "Venereal" and "dysenteric" cases are thus but terms to indicate the foci from which the disease may originate, and I have no doubt that there are other portals of entry.

Finally, apart from the many interlocking clinical features of the whole groups of "rheumatoid" diseases, if we but remember that histological examination of joints from Reiter's disease, "classical" rheumatoid arthritis, psoriasis, arthropatica, ankylosing spondylitis, etc., show exactly similar features, we may wonder why a unitary infective aetiology for this group of disorders has so long been neglected, and, since "psoriasis" must itself be a manifestation of the infection, whether the aetiology of this common dermatological disorder may at the same time be elucidated. In contradistinction, therefore, to the views of Dr. Baron, I believe that the weight of evidence overwhelmingly comes down on the side of Reiter's disease as defined by me above, that a specific organism is responsible for non-specific urethritis (a most misleading term for such a truly specific disease), and that with the discovery of this organism it will be found that the various conditions, classical rheumatoid arthritis, psoriasis, arthropatica, etc., are but syndromes played as variations on the central theme of an infective organism.—I am, etc.,

King's College Hospital, London S.E.5. F. L. LYDON.

Epidural Anaesthesia and Bed Rest in Sciatica

SIR,—It is most interesting to read in your issue of January 28 (p. 286) that your correspondents Mr. F. C. Dwyer and Mr. F. Beddow find that their patients with sciatica are usually completely pain-free after one week's hospital bed-rest on a fracture board and light-weight traction. This is certainly not my usual experience and is obviously an impression on their part, else they would surely have given the figures.

I do not think anybody has ever advocated epidural injections in cases which clinically point to a definite irreducible tear of the annulus fibrosus. There are very definite indications for which cases epidural injections may be given, and one for which this procedure is highly contraindicated.

Mr. Dwyer and Mr. Howard Beddow say glibly that the disk should be removed at operation in those cases of sciatica due to prolapsed intervertebral disk which do not respond to bed-rest and their adjuncts. They do not state which operation they advocate. Is it the anterior or the posterior approach? Do they do a fusion as well? It would be very interesting to know the results of their operations. I find that 60% of my patients are unwilling to undergo such a major operation, and I am most diffident about lightly recommending an operation of which only about 54% are successful.—I am, etc.,

Johannesburg. NORMAN KLASS.

Needle-biopsy Technique in Amoebic Abscess

SIR,—The demonstration by Professor T. Doxiades and his colleagues (February 18, p. 460) of vegetative forms of *Entamoeba histolytica* in a needle-biopsy specimen of liver is of great interest. The application of needle-biopsy technique to the definitive diagnosis of hepatic amoebiasis has been neglected. In practice

the differentiation of a "cryptogenic" from an amoebic liver abscess has rested on combinations of the following criteria: the macroscopic appearance of the contents; evidence of associated amoebic colitis; or the clinical response to a therapeutic trial of emetine or chloroquine.

Because the amoebae are chiefly located in the wall of the abscess, it seemed logical to attempt to secure a biopsy specimen from this area. A deliberate attempt was therefore made to biopsy the abscess wall using a Vim–Silverman needle. To date four patients have been thus investigated without any untoward effects. The rather friable specimens were fixed immediately in 10% formol-saline. In two instances numerous vegetative forms were demonstrated in the sections. Examination of smears of the abscess contents failed to reveal amoebae.

These preliminary results are regarded as sufficiently encouraging to warrant the pursuit of this practice in the routine investigation of liver abscesses.—I am, etc.,

K. J. KEELEY.

Department of Medicine,
Baragwanath Hospital and
University of the Witwatersrand,
Johannesburg.

Relief of Pain by Cooling the Skin

SIR,—I was very interested in the paper of Mr. Maurice Ellis (January 28, p. 250) about the use of cold for the relief of pain. Since 1950 I have used either sprays of ethyl chloride or carbon dioxide snow in many myalgias, sprains, intercostal neuralgias, and periarticular pains.

I named this latter method "cryopuncture." It seems to work both by the effects of freezing and by that of puncture, just like the old Chinese acupuncture, the physiological basis being the release of histamine *in situ*. The tip of the cryocautery has to be applied on the painful spots; snow-like depressions, surrounded by erythematous halos, will appear, and in some cases they are followed by urticarial weals. Relief of pain is often quite dramatic and persistent; some cases need several applications. I have used this treatment on about 400 patients with good results in the majority of them.—I am, etc.,

A. SLIOSBERG.

Paris 19, France.

Pernicious Anaemia in Jamaica

SIR,—Your issue of January 28 has just arrived. I would like to comment on the paper by Dr. K. L. Stuart and Dr. J. E. MacIver (p. 236) entitled "Pernicious Anaemia in Jamaica."

I note with interest that they state that "anorexia, vomiting, and weight loss of varying severity were particularly common features, and were encountered in 7 of the 10 patients." It is well known that these symptoms are uncommon in classical pernicious anaemia, but on the other hand they are extremely common in tropical megaloblastic anaemia associated with the malabsorption syndrome.[1] One cannot help wondering therefore if these were not in fact cases of malabsorption syndrome. Unfortunately the authors do not give details as to how stools were examined for fat to exclude steatorrhoea. Before steatorrhoea can be excluded it is necessary to do a daily estimation of the total fat excretion over a minimum period of four to five days with the patient on a fat intake of 40 to 100 g.

Unfortunately also the authors do not give their range of normal in the Schilling test, nor do they specify the amount of B_{12} that was given in each test dose—a fact of fundamental importance in interpreting the results they give.[2] If it is assumed that they gave a one-microgramme dose, then the results of the test in cases 1 and 5 are somewhat equivocal, showing some improvement in absorption, but not as much as one would like to see in uncomplicated pernicious anaemia. In cases 4, 6, 8, and 9 there is an undoubted improvement in absorption, such as one might expect in true pernicious anaemia. Unfortunately, however, this does not prove that the cases were cases of pernicious anaemia.

In order to diagnose pernicious anaemia, one must show that there is a B_{12}-deficiency anaemia due to a deficiency of intrinsic-factor excretion associated with a gastric atrophy in the absence of other gastrointestinal diseases. We have found several cases of tropical malabsorption syndrome with histamine-fast achlorhydria, gastric atrophy, and normalization of vitamin-B_{12} absorption on giving intrinsic factor, but in all of whom there was other evidence of intestinal disorder—either a steatorrhoea proven by fat balance, an abnormal xylose absorption, a flat glucose tolerance, abnormalities in the barium-meal picture of the small intestine, or changes in the jejunal mucosa on biopsy study.[3]

In other words, one suspects that at least some of the authors' patients are cases of "tropical malabsorption syndrome" with secondary intrinsic-factor deficiency. The fact that cord changes were seen in these patients is of course related only to their serum-B_{12} levels, and does not support the diagnosis of pernicious anaemia. Subacute combined degeneration of the cord has been seen in patients with tropical malabsorption syndrome. Similarly a sustained response to vitamin-B_{12} therapy alone is a characteristic feature of B_{12}-deficiency anaemia associated with the malabsorption syndrome.[4]

It is very important to realize that there may in fact be little or no difference between the clinical and laboratory findings in patients with megaloblastic anaemia associated with the malabsorption syndrome (or "nutritional megaloblastic anaemia") and those with classical pernicious anaemia, unless full investigations are done. Many of the cases recorded in the literature, and quoted by the authors, cannot be considered as proven cases of pernicious anaemia judged by these criteria.—I am, etc.,

S. J. BAKER.

Department of Haematology,
Christian Medical College, Vellore.

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Fathers at Delivery

SIR,—The hall-mark of good nursing and good doctoring is to consider the needs, wishes, and feelings of the patient as of overriding importance. These wishes should always be met unless they are clearly detrimental to the health of the patient. If this axiom was really kept in mind (unfortunately it is so often forgotten), then the many rigid useless rules that govern the running of our hospitals would soon disappear with a consequent increase of happiness both for staff and patients. This lesson we have learnt in mental hospitals, and the sooner it becomes widespread in general and maternity hospitals so much the better. If, therefore, a mother wishes her husband to be present at the birth of their child, because it is his as well as hers, this wish should be granted gladly. To refuse is cruel and may cause considerable psychological suffering.

As a consultant psychiatrist, and chairman of the Leicester and Leicestershire Branch of the Association for the Improvement of the Maternity Services, I therefore welcome and support the letters by Dr. R. J. Jarrett and Mrs. Jean Taylor (March 11, p. 744).

Finally, I should like to emphasize that the right place for a baby to be born is at home. I deplore the present trend towards encouraging mothers to have their babies in hospital. A mother should only be confined in hospital if it is absolutely necessary for very valid social or obstetric reasons. This view is supported by a recent article by Elias-Jones, Gordon, and Whittaker,[1] which points out that the incidence of neonatal staphylococcal sepsis is 13% in babies born in hospitals and only 4% in babies born at home. The writers say: "When the choice of place of delivery is dictated solely by less substantial reasons, such as domestic or social convenience, the relative freedom from risk of staphylococcal infection of the baby born at home must surely be considered. For those mothers who, for a valid reason, should be confined in hospital the recently canvassed idea of hospital confinement followed by lying-in at home has much to commend it." A mother who has her baby at home is in a much healthier psychological climate. If she has to go to hospital for the actual confinement, the sooner she is back again in this psychological climate the better. Of course there will be exceptions, but exceptions only prove the rule.—I am, etc.,

The Towers Hospital, Humberstone, Leicester. H. B. KIDD.

REFERENCE

[1] Elias-Jones, T. F., Gordon, I., and Whittaker, L., *Lancet*, 1961, **1**, 571.

SIR,—I wonder how many doctors bring their own babies into the world. More than 70 years ago my father delivered both his children (though, as I was the younger of the two, I have no definite recollection of either event). I believe he thought he was the best obstetrician in the town, and the only one good enough for his wife. Not a bad reason. I dare say he was right.—I am, etc.,

St. Brelade, Jersey. NORMAN A. SPROTT.

*** This correspondence is now closed.—ED., *B.M.J.*

Cysticercosis

SIR,—By reading the closing remark, "It is also important to remember that human cysticercosis is not caused by eating measly pork," in the annotation on cysticercosis (March 18, p. 804) one should not get the impression that it is not possible to develop human cysticercosis by eating measly pork. It is a known fact that if man ingests raw or inadequately cooked pork containing the infected larvae (cysticerci), the larval stage may parasitize in the intestine of man and may subsequently become an adult worm. A gravid segment containing numerous eggs can be carried back into the stomach and upper intestine by retroperistalsis, and the liberated eggs containing the embryos can penetrate the bowel-wall causing cysticercosis, and can sometimes lead to heavy infestation. One should therefore be very careful not to eat raw or inadequately cooked pork in an endemic area in order to avoid the risk of developing cysticercosis. This is possibly not the source of infection in Great Britain, as measly pork probably does not occur nowadays.—I am, etc.,

Wordsley Hospital, Wordsley, Worcs. B. BANERJEE.

New Cases of G.P.I.

SIR,—I have been very interested in the correspondence on new cases of G.P.I. (January 21, p. 206; March 11, p. 742). We have noted that taboparesis is a more common disease at the present time than would be expected.

A woman aged 61, recently referred to our department, was sent in as a case of senile confusion with hypertensive congestive heart failure and also gave a history of occasional blackouts. On examination she had a double aortic murmur and her C.S.F. showed a strongly positive W.R. at all dilutions, and also an increased globulin and an abnormal paretic Lange curve. She was treated with one million units of penicillin for 10 days. There was great improvement clinically and also some visual improvement. She came to the geriatric department three months later with an ulcer of the leg, the margin of which was hard, rigid, raised, and indurated. This ulcer proved indolent and has now healed.

Another woman aged 77, referred to this department in hypertensive congestive cardiac failure, was found to be a case of taboparesis and showed mild ataxia and a double aortic murmur. *X*-ray examination revealed the presence of an aortic aneurysm. She exhibited intermittent confusion and showed a positive W.R. in the C.S.F.

A third case, a woman of 79, was referred to us as a case of paraplegia of 10 years' duration which exhibited also amyotrophy of both arms and delusions of the grandiose type. There were sensory changes in the upper limbs and a pronounced intention tremor. The C.S.F. showed an increased globulin and a positive W.R. reaction together with a paretic Lange curve.

—I am, etc.,

Wrexham, Denbighshire. I. P. ROWLANDS.

Marking the Skin

SIR,—Mr. R. Rowden Foote's letter (March 18, p. 830) raises a point of practical importance in many branches of medicine. Although the requirements for preoperative marking may well differ from those in dermatology, I should like to mention an alternative method that I have found very satisfactory for a number of years, particularly in marking intradermal tests and patch-tests after the patch has been removed at 48 hours. This consists of the use of an ordinary blue or black ball-point pen, afterwards covering the marking with a light spray of "nobecutane." This stays in position, undisturbed by washing or friction, for at least 48 hours, but it can be peeled off before that time if necessary. The marking comes away with the plastic film. I have never met any undue reaction from this method, nor does it affect any adjacent test areas. Vinyl acetate sprays are, of course, used widely in surgery for wound dressings.

I should add that I agree with Mr. Foote that not all ball-point pens write easily on the skin. I use one of the cheapest type and find it very satisfactory (the pen should be used sloping downwards, of course, or the smooth flow of ink will stop. I should also add that red and green marking pens should never be used. I remember being called to see a patient on whom widespread preoperative markings had been drawn in red; the patient was sensitive to the dye and produced a contact dermatitis along the line of all the marking. Patch-tests were positive to red and green inks, but not to blue and black. I have never seen any contact dermatitis from these latter colours.—I am, etc.,

London W.1. D. S. WILKINSON.

Basic Psychology

SIR,—Stengel[1] has pointed out that the student comes to clinical psychiatry without the same background of basic science from which other branches of medicine reap their applied rewards, but he does not suggest that the psychology of animal behaviour should be an important part of biological teaching in the first year of medical training. Surely a grounding in the principles of ecology cannot be instilled too early. To watch dogfish feeding by smell, for example, rather than by sight must make their large olfactory organs, evident on dissection, more meaningful.—I am, etc.,

Dartford, Kent. J. P. CRAWFORD.

REFERENCE

[1] Stengel, E., *J. ment. Sci.*, 1958, **104**, 772.

Varicocele

SIR,—May I submit that your leading article on varicocele (March 18, p. 801) is quite unacceptable to anyone who has studied this matter from an evolutionary point of view? I have tried to show, in a small work[1] on varicose veins and varicocele, which you were good enough to review last year (October 29, p. 1293), that the cause of these conditions lies solely in stasis in the left descending and iliac colon, due to our present consumption of refined flour and sugar, and that there is no other cause whatsoever. I based my argument on three separate considerations. The first concerns the evolution of the human body, and is theoretical in nature, though in my opinion this piece of evidence is unassailable. The second is that the incidence of these conditions in this country far exceeds that of any congenital abnormality. For example, even varicose veins, which are open to a more accurate assessment in diagnosis than varicocele, are about ten times commoner than any known congenital malformation. The third consideration is the racial one. I showed in my work that varicose veins and varicocele have been carefully established as absent in natives still living under natural conditions. For example, in the natives selected in my work—those living in a tribal manner in Africa—field surveys carried out for parasitic and infectious diseases have carefully recorded all surface abnormalities. Thus, the incidence of hernias quoted by Kinnear Brown,[2] Government leprologist, was quoted with great accuracy, but varicose veins and varicocele were so rare that they could not be recorded at all. Per contra, these conditions are by no means uncommon in negroes in Africa when they live under Westernized conditions, and in negroes in Chicago and New Orleans they are as common as in the white races. These arguments are elaborated in my work, and render a congenital cause for either condition quite untenable. Exactly the same is true of haemorrhoids.

It is true that certain persons are more vulnerable to the primary cause than others are, which can easily be explained by individual variations in the relation of the colon to the veins concerned, but this individual vulnerability is absolutely different from primary causation. One hundred feet can go into pointed shoes, and only a moderate percentage will end up with clinical hallux valgus. The individual vulnerability explains this percentage figure, but the primary cause—the pointed shoe—alone explains why the condition occurs at all. The absence of venous conditions in the tribal natives mentioned presents a perpetual challenge to the causation and line of action expressed or implied in your leading article.

Under modern conditions, an operation attempting cure may be preferred to a removal of the cause achieving prevention and arrest. This is true of varicocele no less than of varicose veins and haemorrhoids, but no one who thoroughly understood the true causation of this condition would, I submit, prefer the former solution, if only for the reason that other conditions may be prevented simultaneously, as suggested in my work. Rather would such a one prefer to keep his varicocele so as to serve as an index of his adherence to a more natural form of food consumption. It is clear that in exceptional cases, such as very large varicoceles or those accompanied by sterility, surgery might be invoked as well. But, as regards the controversial part played by varicocele in sterility, the very alteration in food-consumption that removed the cause in the one might well do so in the other.—I am, etc.,

Lee-on-Solent, Hants. T. L. CLEAVE.

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[1] Cleave, T. L., *On the Causation of Varicose Veins and their Prevention and Arrest by Natural Means. An Evolutionary Approach*, 1960. John Wright and Sons Ltd., Bristol.
[2] Brown, J. A. K., *East Afr. med. J.*, 1956, **33**, 19.

Compulsory Wassermann Test Before Marriage

SIR,—I was extremely interested in Dr. C. S. Nicol's article (February 18, p. 445) on the recrudescence of venereal disease, especially in regard to syphilis. He states that the figures for syphilis have continued to decline—namely, from 8,432 new cases in 1951 to 3,927 in 1959. This is still more than 10 cases per day—a figure that can be reduced even further by a simple and sensible law.

One is aware that in the United States of America no couple can enter into matrimony until both husband and wife produce a certificate from a recognized laboratory to the effect that the serological test for syphilis is negative. Furthermore, the likelihood of congenital syphilitics being born will be reduced to a bare minimum. Surely we can learn a simple lesson from the New World, and all civilized countries should follow suit and pass a similar compulsory law.—I am, etc.,

Johannesburg. HERBERT KRAMER.

Case of Situs Inversus

SIR,—Last December a post-mortem examination was done on a man aged 60 who had died from coronary thrombosis involving the proximal part of his right coronary artery. This case was interesting because the man had situs inversus. His coronary thrombosis had been accompanied by pain down his right arm. Apparently he had been in congestive cardiac failure on and off for some years, and in the early and middle part of his life had suffered from attacks of rheumatic fever.

There was a lung with three lobes on the left side of the chest and a lung with two lobes on the right. The heart lay on the right side and was markedly enlarged. The aorta was on the right, and the left subclavian and left common carotid artery arose from the innominate artery. The inferior and superior venae cavae lay on the left side of the vertebral column and the aorta on the right. Both diaphragms were intact. The stomach

was on the right, the liver and gall-bladder on the left, the equivalent of the left lobe of the liver lying under the right diaphragm. The duodenum was reversed so that it, together with the underlying pancreas, lay on the right side of the abdomen, as also did the spleen. The genital organs were normally developed. There was no congenital abnormality of any organs. Dissection of the heart showed the cusps of the mitral valve to be partly thickened and distorted. The aortic valves were also thickened and were partly fixed, the valve being incompetent.—I am, etc.,

Kingston Hospital Pathological Laboratory, Kingston-upon-Thames, Surrey. M. H. COX.

Oestrogen Excretion in Breast Cancer

SIR,—We would like to support Dr. Anthony Green (March 25, p. 904), as we have found vaginal smears extremely sensitive indicators of the sex hormones.

However, we feel this vexed question as to how the cornification index compares with the urinary excretion of oestrogens requires some clarification. In the first instance we think it is unwise to assess oestrogen by the cornification index alone without taking into account the amount of cell desquamation, the size, pattern, and type of cells present. Experience has shown that a study of all these factors indicates whether one is dealing with oestrogen alone or in combination with progesterone and/or androgen. In the former we find a very good correlation between the cornification index and the excretion of urinary oestrogens; in the latter case relatively large amounts of these anti-oestrogenic hormones will naturally reduce the cornification index, although the smear will still show a mixed hormone picture. This might explain why in some of the cases reported by Dr. G. I. M. Swyer and his colleagues (March 4, p. 617) the cornification index did not correlate with the urinary oestrogens. In other words, vaginal smears reveal more than just oestrogen.

We would like to stress that the aim of the endocrine cytologist is *not* to replace all other forms of investigation but rather to add his findings to those of his colleagues. Surely it is the patient with a high excretion of urinary oestrogens and a low cornification index who should be selected for further biochemical investigation rather than dismiss the cytological findings as unreliable.—We are, etc.,

M. MURRAY.
F. OSMOND-CLARKE.

Endocrine Cytology Unit, Chelsea Hospital for Women, London S.W.3.

SIR,—Before venturing to comment on the paper by myself and colleagues (March 4, p. 617), Dr. Anthony Green should have taken the trouble to read it carefully. Our report was based not on 10 cases, as stated in his letter (March 25, p. 904), but on 24. I presume he has obtained the figure 10 by looking at half of Table II. Perhaps he would now do us the honour of looking at the rest of that table and of reading the rest of the paper.

He will see (*inter alia*) that, while a comparison of 116 vaginal smears with the corresponding urinary oestrogen excretion gave a correlation, it was of a rather low order, especially in the intermediate ranges. Unless he has made similar or, better still, more extensive comparisons, it seems to me irrelevant that his laboratory has studied thousands of vaginal smears—these studies will neither refute nor confirm our findings unless they have included urinary oestrogen determinations. We concluded that single vaginal smears were unlikely to provide a reliable index of oestrogenic status in patients of the kind we were studying, and I do not think he can quarrel with that.

The principal object of our investigation was to see if the changes in the excretion of certain oestrogens brought about by oophorectomy with or without adrenalectomy bore any relation to the clinical course of the breast cancer, and whether the pre-operative oestrogen excretion might offer any indication of likelihood of response to ablative surgery. We concluded that our studies were unrewarding in both respects—and in this we concur with other authors. Why then, Sir, should it be necessary for Dr. Green to caution your readers about our paper?—I am, etc.,

London N.W.1 G. I. M. SWYER.

Clinical Aspects of Cardiomyopathy

SIR,—Dr. J. F. Goodwin and his colleagues, in their definition of cardiomyopathy (January 14, p. 69), use the words "a subacute or chronic disorder of heart muscle of unknown or obscure aetiology. . . ." In their third paragraph they state that "no attempt has been made to give a full classification of all causes of cardiomyopathy." Surely, if their definition means anything, a disease in which there is a known cause of cardiomyopathy cannot fall within the group that they are describing. Thus, Case 1, for instance, is a clear-cut example of scleroderma with cardiac involvement, and does not merit inclusion under a classification of unknown or obscure aetiology. Perhaps the word "obscure" is the key, but I suggest their definition of cardiomyopathy would be more precise if it contained no reference to aetiology.

I am also disturbed that in a ten-page paper entitled "Clinical Aspects of Cardiomyopathy" the following statement should appear (p. 70) under Type 1: "but the overall clinical picture will be made the subject of a more detailed report later." I suggest that if there were more details to be supplied this was the paper in which they should have been given. There is too much repetition already in medical writing.—I am, etc.,

Christchurch, New Zealand. D. R. HAY.

Medicine Broadcast

SIR,—I, too, want to register my disapproval of broadcast medicine and surgery. If childbearing and life-saving surgery are fit subjects for entertainment, then so also are death and disposal of the corpse. Sooner or later there will be a death on the table. Let us have a television camera in the crematorium chamber, and spare not even the skeletal pulverization without which the ashes would not fit into the urn.—I am, etc.,

Gobowen, Salop. R. P. W. KUP.

SIR,—I would like to join those who have written to support Dr. G. D. Jones (March 11, p. 750) in his protest against the use of dramatized medicine and surgery as material for television entertainment.

"Sometimes to cure, often to relieve, and always to comfort" is, I believe, a fair epitome of the aims and outlook of most of us. This letter is prompted by the distress caused to a lay acquaintance who suffers from Parkinsonism and who saw a recent programme in which diathermy destruction of the affected region of

the brain was demonstrated. I wonder how many similar patients, or, to take another example, how many parents of children suffering from congenital cardiac lesions derived any comfort from these technical demonstrations. It is surely expecting too much to suppose that patients and those to whom they are dear can view these procedures objectively.

While it is obviously our duty to ensure that each of our patients, together with his relatives, understands what modern medicine has to offer in his particular case, there can be no justification for making a spectacle of dramatic treatments which are horrific to some or which may give rise to false hopes in others.—I am, etc.,

Bristol. G. A. DALTON.

SIR,—I suspect that Dr. G. D. Jones (March 11, p. 750) and those who have supported him (March 25, p. 900) have really been born too soon and in the wrong part of the world. They are witch-doctors and medicine-men at heart who believe that medicine should be shrouded in mystery and patients only told what the doctor thinks it is good for them to know.

The day of this sort of mumbo-jumbo medicine is over and more and more patients are taking an intelligent interest in their treatment. It is to us in the medical profession to whom they turn for enlightenment and it is for us to give it to them. Programmes such as the "Your Life in Their Hands" series are an admirable means of educating the public and keeping them (and some of us) in touch with recent advances in treatment. These programmes may also help in the recruitment of nursing staff and they certainly enhance the prestige of the profession. We are often taunted with our inability to cure the common cold, but at least it is well that the public should know that we can deal with an atrio-ventricular defect.

Perhaps the greatest good that these programmes do is to demonstrate to the public just how complicated modern treatment has become, how much team-work and expensive equipment are required, so that they realize that they are getting value for the money, their money, that is spent on the N.H.S. I enjoyed the series "Your Life in Their Hands" and I think the producer and his team are to be congratulated on the manner in which they were presented, and I hope we have more.—I am, etc.,

Hove 2. REX BINNING.

Scorpion Stings

SIR,—Out of 78 cases of scorpion sting seen during the last 14 years in Managaon Taluka, Kolaba District of Bombay State, 23 died, including 9 adults. This is contrary to my experience elsewhere in Bombay State, Ceylon, and Aden, and to the general opinion held by many workers.[1–5]

The scorpions here, though not yet identified, do not have any distinguishing appearance. Stings in November and May are particularly serious. Following the sting there is local redness, sweating, severe pain and burning soon followed by shock-like condition, marked weakness (without paralysis), bradycardia (pulse-rate up to 36/minute), and fall of body temperature. About 4 to 6 hours later there is profuse perspiration, the sweat literally flowing from the body, the patient is anxious and restless and pulse rate is 140–160/min. Within 2 to 10 hours pulmonary oedema sets in, there are bubbling rales all over the chest with dyspnoea and hurried, shallow respiration. The patient coughs up copious blood-tinged, watery, frothy expectoration without exertion. If first seen at this stage the outcome is invariably fatal, occurring within 4 to 72 hours after the sting.

Analysis of 20 Fatal Cases

Age	Sex		Average Time (hr.) between Sting and Death
	M	F	
0–5	4		4
6–10	3	2	14
11–15	4		14
Over 16	9		29

Morphine, atropine, glucose saline, and glucocorticoids with antibiotics form the usual treatment. Death in adult patients and the presence of pulmonary oedema are the two outstanding characteristics of this series. Children are generally believed to suffer seriously after scorpion sting.[1–3 5] Pulmonary oedema is not commonly mentioned and perhaps remains unexplained.[1 6]

Specific antiserum is not available. Though anti-snake-venom serum is supposed to be of some use[1] it has not been tried so far. I would be grateful to receive the comments of your readers.—I am, etc.,

Goregaon, D. Kolaba, Bombay State, India. P. M. MUNDLE.

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Keeping the Plaster Dry

SIR,—Many patients who, for whatever reason, have part of a limb encased in plaster-of-Paris complain bitterly of not being able to have a bath in reasonable comfort. "The plaster must be kept dry," they are told. For some time I have advised such patients before they bath to pull over the plaster a polythene bag of suitable size and of a length extending a few inches proximal to the plaster, then with a rubber band encircling the limb the plaster is made waterproof.

Other surgeons may have used this simple and efficient method of keeping the plaster dry, but I have not seen it recorded. In such frequent and distal injuries as Colles's and Pott's fractures, etc., it is applicable and appreciated.—I am, etc.,

Dundee. F. R. BROWN.

More Market Research

SIR,—This morning I had my surgery interrupted by a representative from a body calling itself the Medical Market Research Services. "I won't keep you a minute, sir. Could I just ask you a few questions?" We are all familiar with the random-sample interview technique in everything from politics to polishers. The questions rolled on: "Isn't it correct to say that you see five to six cases of backache every week? . . . Please look at this list—do you prescribe any of these preparations? . . . Yes, No, Don't know? . . . Why not?" My reply was that I regarded the questionary and its

presentation as impertinence, as grossly unethical, and as worthless as a method of clinical or any other assessment.

It is one thing for a manufacturer's representative to call on us to present and discuss his products, but the use of straight market research methods introduces a new boorishness altogether in the approach of the drug industry to the profession.—I am, etc.,

London N.W.2. S. GOLDWATER.

Selection of Medical Students

SIR,—Dr. D. L. J. Bilbey (March 11, p. 743) enumerates at some length the problems of selecting women medical students. Any G.P. who employs an assistant is familiar with these same problems of selection. There is no obligation on a medical school to give any reason for the rejection of a particular candidate. In the case I quoted (December 24, p. 1890), however, the reason given is so obviously untrue that there is bound to be "some doubt and dissatisfaction with regard to the present methods." (I quote from Dr. Bilbey's letter.) It is this fact which needs emphasis and which leads to speculation as to the "true reasons."

May I again, as this case is a personal one, sign myself just "PUZZLED."

Deficit of Doctors

SIR,—The recent correspondence on the shortage of doctors and your leading article (March 25, p. 883) on the medical staffing of hospitals make an interesting comparison with the suggestion contained in the section on medical manpower of the 1957 report of the Ministry of Health.[1] This gives the findings of the Willink Committee,[2] which reported that after 1961 a reduced output of new doctors from medical schools would suffice to meet all likely needs, and suggested that in consequence the student intake should be reduced by one-tenth as soon as practicable. One hopes that the Platt Committee's findings and conclusions will prove to be of more lasting value.—I am, etc.,

Gaydon, Warwicks. G. R. C. ATHERLEY.

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1 *Report of the Ministry of Health for the Year Ended 31st December, 1957*, Part 1. H.M.S.O., London. Price 12s. net.
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POINTS FROM LETTERS

Oral Contraception

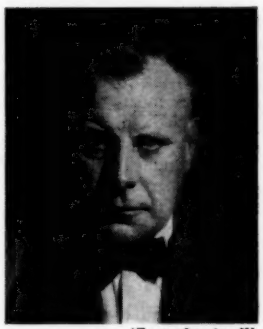
Dr. GABRIEL V. JAFFÉ (Bournemouth) writes: If we are to look forward to a world where children are born by choice only, as Dr. E. Elkan (March 4, p. 673) advocates, contraception is only one factor involved. Social, religious, ethical, and economic aspects often conflict, making an unequivocal choice impossible. . . . Once contraception is accepted for whatever reason, the advent of a safe, simple, inexpensive, effective tablet unrelated to the sex act itself as opposed to direct unaesthetic mechanical protection, is an inestimable benefit to mankind. Will promiscuity increase as a result of easy oral contraception? If fear of pregnancy is at present a deterrent, albeit frequently a subconscious one, only when that fear is removed will moral and spiritual values come into their own as promoters of chaste behaviour and inhibitors of irresponsible sexual freedom with its distressing psychological consequences.

Obituary

HAMILTON BAILEY, F.R.C.S., F.A.C.S.

Mr. Hamilton Bailey, emeritus surgeon to the Royal Northern Hospital, London, and author of a number of famous surgical textbooks, died on March 26 at Malaga, Spain, where he retired during the winter months, after a succession of operations. He was 66 years of age.

Hamilton Bailey was born at Bishopstoke, Hampshire, on October 1, 1894, the son of Dr. H. J. Bailey, of Brighton. From St. Lawrence College, Ramsgate, he went on to study medicine at the London Hospital, where he won prizes in physiology and clinical medicine. At the outbreak of the first world war he went out to Belgium as a dresser with the first Belgian unit of the British Red Cross Society. Taken prisoner, he was later repatriated and then served as a surgeon probationer in the R.N.V.R. Returning to the London Hospital, he qualified L.M.S.S.A. in 1916, held a resident post as a house-surgeon, and then served for the rest of the war as a temporary surgeon in the Royal Navy in H.M.S. *Inflexible* and Monitor 19.



[*Fayer, London W.*

Having taken the F.R.C.S. in 1920, Mr. Bailey became surgical registrar and tutor at the Liverpool Royal Infirmary, and demonstrator of anatomy at Liverpool University. He then returned to the London Hospital as surgical registrar and, later, as first surgical assistant. He received a B.M.A. research grant in 1925 and for the two following years he held the Gillson scholarship of the Society of Apothecaries. He was then appointed assistant surgeon to the Liverpool Royal Infirmary, but, resigning from this post, he became resident surgeon at the Dudley Road Hospital, Birmingham. After a short time on the staff of the Bruce Wills Memorial Hospital in Bristol, he came back to London and was elected to the staff of the Royal Northern Hospital, in charge of the genito-urinary department. In the course of time he joined the staff of several other hospitals, including the Italian Hospital, the Clacton Hospital, and the Metropolitan Ear, Nose, and Throat Hospital (as general surgeon). He was also surgeon and urologist to the Essex County Council, and he was an external examiner in surgery to the University of Bristol. A Hunterian professor at the Royal College of Surgeons, he was a Fellow of the American College of Surgeons, a member of the Société d'Urologie, and a vice-president of the International College of Surgeons.

Hamilton Bailey was probably the best-known surgical author in Britain; his books have been translated into many languages and enjoy a wide circulation in North America. An entire edition of *Surgery of Modern Warfare* was purchased during the second world war for distribution to medical officers in the armed Forces of the U.S.A. Other notable books include *Physical Signs in Clinical Surgery* (13 editions), *A Short Practice of Surgery* (written with Mr. R. J. McNeill Love), and *Pye's Surgical Handicraft*, of which he was editor. His *Notable Names in Medicine and Surgery*, written with Mr. W. J. Bishop, was published in 1959.

His main relaxation was swimming, and when he changed his residence he always had a swimming-pool constructed in the grounds, which he used all the year round. His only son was killed in a railway accident when a schoolboy. We

extend our deep sympathy to his widow, who so ably encouraged and helped him with his literary achievements.

R. S. S. writes: A year ago, when Hamilton Bailey reached retirement age, he bought a house on the hills outside Fuengirola, between Malaga and Gibraltar, where he meant to spend his life writing and editing new editions of his successful surgical books. Just over a month ago he came as a patient to the Colonial Hospital, Gibraltar, with vague but disquieting abdominal symptoms. They disappeared, however, in a few days; *x* rays revealed nothing of note, and he insisted on returning home, with the proofs of a new edition of *Pye's Surgical Handicraft*. In a couple of days he developed an acute obstruction, and the local doctor sent him urgently into a surgical clinic in Malaga, where he had in succession four abdominal operations. He declined to have a colleague flown out from England, and discussed his symptoms and treatment frankly with his surgeon and with his wife, who did not leave the clinic, day or night, for a month. He was desperately ill, but was able to speak to friends from Gibraltar, and everyone who knew him must regret that his gallant fight for life should have ended in defeat. Hamilton Bailey was a great character, a giant of a man who worked himself, his assistants, and his three secretaries to a standstill. No one of his generation had more influence on the teaching of surgery to medical students and young postgraduates—how absurd now it seems that he was never elected to the staff of a teaching hospital in London—and this influence is bound to persist for a long time.

J. J. HARPER NELSON, C.I.E., O.B.E., *M.C.*, M.D. F.R.C.S.Ed., M.R.C.P.Ed.

Colonel J. J. Harper Nelson, who died at his home on the Isle of Mull on March 10 in his eightieth year, was a well-known and beloved figure in the Punjab, where he worked for many years as a teacher of therapeutics and medicine, as a widely consulted physician, and as Principal of the King Edward Medical College, Lahore.

The son of the Rev. J. Nelson, John Joseph Harper Nelson spent his childhood in Australia and India. Having received his earlier education partly in India and partly in London, Nelson entered Edinburgh University, where his outstanding ability soon manifested itself. He graduated M.B., Ch.B., with first-class honours, in 1907, and entered the Indian Medical Service as a lieutenant in 1908. During study leave he proceeded M.D., again with first-class honours, in 1913, and took the Fellowship of the Royal College of Surgeons of Edinburgh. In the first world war he went to Mesopotamia with the first detachment of troops, took part in some of the earliest and bloodiest battles, and greatly distinguished himself. He was awarded the *M.C.* and was mentioned in dispatches four times—being appointed O.B.E. later when D.A.D.M.S.(San.) in Bagdad.

Soon after the cessation of hostilities he joined the staff of the Lahore Medical College and remained there as physician and professor of materia medica, therapeutics, and, finally, medicine until his retirement in 1937. He took a very lively interest in the affairs of the students, encouraging them particularly in sporting and dramatic activities. In his latter years as Principal he was greatly looked up to and respected by all—Europeans and Indians alike. He took the M.R.C.P.Ed. in 1934.

Appointed C.I.E. on his retirement he returned to Scotland in 1937, but soon realized that his heart belonged to India and obtained the appointment of director of health services in Kashmir, where in the short space of time available to him he reorganized the medical services and designed several hospitals. The outbreak of the second world war led to his recall to service as consultant physician with the Forces in Iraq. The end of hostilities saw him actively engaged in U.N.R.R.A., and finally he served with Pensions Appeal Tribunals for some years. He was also a member of the Central Council of the B.M.A. for two or three years, having previously been honorary secretary and later president of the Punjab Branch.

In his eventual retirement, with the rank of colonel, Harper Nelson entered heartily into the social life of Mull, where he will be greatly missed. Throughout his adult life he was an ardent Mason. During the last two years he was an invalid, and, latterly, bedridden but in no pain. His presence was greatly missed at the recent Jubilee celebration of the Lahore Medical College, which he had done so much to build up and foster.

He married in 1909 Annabella, daughter of N. L. MacCormick, of Fionnphort, Isle of Mull, and she survives him, together with a son and two daughters.—G. R. McR.

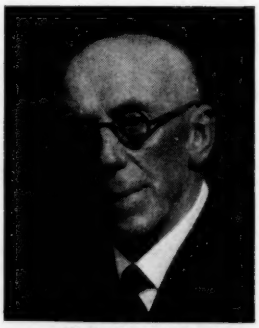
Dr. DOUGLAS GUTHRIE writes: Those of us who were privileged to be his fellow students in Edinburgh more than half a century ago, and also the many students who were his pupils and colleagues in India and Pakistan during more recent years, will mourn the passing, and yet revere the memory of, John Joseph Harper Nelson. His father was a Presbyterian padre on the Indian Military Establishment, and when he himself entered the Indian Medical Service in 1908 it soon became apparent that his ability was not merely of the academic variety; in his choice of a career he had acted wisely.

No account of the manifold activities of this gallant officer would be complete without some reference to the man himself. His kindness of heart and his love of humanity, so obvious to all his friends, were no assumed virtues, but were in accordance with the deeply religious principles which controlled all his thoughts and actions. His was no semblance of piety, for he hated cant, but rather a deep conviction of goodness and truth which he so unconsciously imparted to others. Those who remember him as an Edinburgh student in bygone days can readily understand why he became so highly respected in the East, and why so many recall his influence with gratitude. Indeed, Harper Nelson's career, in all its phases, showed very clearly that, to be a good doctor, one must first be a good man. To his widow and children we extend our sincere sympathy.

E. D. TELFORD, M.Sc., F.R.C.S.

Professor E. D. Telford, professor emeritus of systematic surgery in the University of Manchester, died at his home at Prestatyn, Flintshire, on March 26. He was 84 years of age.

Evelyn Davison Telford was born in Yorkshire, near Middlesbrough, on June 16, 1876, and was educated at Manchester Grammar School. From there he went on to Gonville and Caius College, Cambridge, with an entrance scholarship, and later a foundation scholarship, and took first-class honours in Part 1 of the Natural Sciences Tripos. Completing his clinical training at Manchester, he took the London Conjoint diploma in 1900. He was a house-surgeon at Manchester Royal Infirmary in 1901, and then became surgical registrar and tutor. In 1903 he took the F.R.C.S. and graduated B.Chir. He was granted the Manchester M.Sc. in 1929. From 1903 to 1905 he served as resident surgical officer at the Manchester Royal Infirmary, and during this time showed himself to be a surgeon of undoubted skill, careful technique, and sound judgment. On the completion of his hospital residence he was appointed to the honorary surgical staff of the Royal Children's and Salford Royal Hospitals. These posts led to his election to the honorary staff of Manchester Royal Infirmary in 1908.



[*F. W. Schmidt, Manchester*

The care and treatment of crippled children was one of his great interests, and he was visiting surgeon to the

special schools under the Manchester education committee at Swinton. Later he was appointed by the Manchester corporation as visiting surgeon to its children's hospital for tuberculosis at Abergele, which was opened in 1931. Two years later, on the death of Sir Robert Jones, he was appointed consulting surgeon to the children's wards in the hospital of the North Wales branch of the Welsh National Memorial Association at Denbigh.

After serving in various lectureships in surgery in Manchester University, Telford was appointed professor of systematic surgery in 1922, on the resignation of J. W. Smith. He occupied the chair until 1936, when he retired and the title of professor emeritus was conferred upon him. He contributed many papers to the literature, especially articles describing the surgical treatment of crippled children, and his book, *The Problem of the Crippled School Child*, dealt not only with the treatment of these children but also with their education.

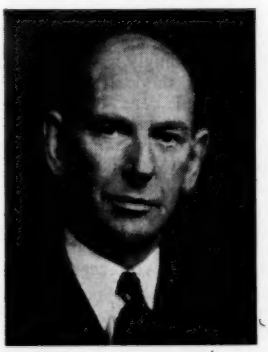
In his later years at Manchester Royal Infirmary Telford became keenly interested in the effect of sympathectomy on vascular disorders. In this work he had the co-operation of his colleague, the late Lord Stopford, then professor of anatomy in the university. An important initial observation was on the prognostic value of spinal anaesthesia in vaso-spastic diseases of the lower limbs, on which he and Professor Stopford contributed a paper to this journal in 1932. Two other contributions, also written in collaboration with Professor Stopford, appeared in this journal in 1933, one on lumbar sympathectomy in thrombo-angiitis obliterans, and the other on sympathectomy in anterior poliomyelitis.

Professor Telford was quiet in manner, unassuming, and a man of few words, but what he said always carried weight, and he was a popular teacher. An examiner in surgery for the Universities of London and Cambridge, he was a past-president of the Manchester Medical Society, and at the Annual Meeting of the B.M.A. in Manchester in 1929 he was president of the Section of Surgery. On his retirement he went to live at Prestatyn. He leaves a widow, formerly Miss Sarah Waterhouse, whom he married in 1909.

R. A. LENNIE, M.D., LL.D., F.R.F.P.S., F.R.C.O.G.

Emeritus Professor Robert A. Lennie, who held the Regius Chair of Midwifery at the University of Glasgow, died at his home in Helensburgh on March 26. He was 72 years of age.

Robert Aim Lennie was born on April 5, 1889, and was educated at the High School of Glasgow and Glasgow University, where he graduated M.B., Ch.B. in 1912. He was appointed to the staff of the Glasgow Royal Maternity Hospital in 1914, but on the outbreak of war he joined the R.A.M.C., in which he served till the end of hostilities. He was in command of the Desert Ambulance Train and was mentioned in dispatches. On returning to civil life he resumed his post at the Maternity Hospital and became a member of the gynaecological staff of the Victoria Infirmary. In 1934 he was appointed obstetrician in charge of wards in succession to the late Professor J. M. Munro Kerr at the Maternity Hospital, and gynaecologist to the Victoria Infirmary.



A keen Territorial since the first world war, on the outbreak of the second world war he was given the charge of No. 4 Scottish General Hospital—later the Military Hospital, Drymen—where he served until recalled to civilian life by the Department of Health for Scotland, where his services were urgently required. He resumed his duties in the Maternity Hospital and Victoria Infirmary, and also took charge of the gynaecological department of the Emergency Medical Services Hospital at Bangour.

Professor Lennie was appointed to the Regius Chair of Midwifery at Glasgow University in 1946, and shortly afterwards severed a long connexion with the Victoria Infirmary and took charge of the gynaecological department of the Western Infirmary adjacent to the University. On his retirement six years ago the University conferred on him the degree of LL.D. and the title of emeritus professor.

In his professional career, Professor Lennie was elected a Fellow of the Royal Faculty of Physicians and Surgeons, Glasgow, in 1926, proceeded M.D. in 1928, and was elected a Founder Fellow of the British College of Obstetricians and Gynaecologists in 1929, and served on its council from 1929 to 1935, becoming F.R.C.O.G. in 1936. Although not a prolific writer, he was the author of original articles of note and contributed to textbooks, one of the subjects of greatest interest to him being the management of difficult obstetric cases. He received many distinctions, having been president of the Glasgow Obstetrical Society, Honorary Fellow of the Edinburgh Obstetrical Society, chairman of the Central Midwives Board of Scotland, and Colonel Commandant of the St. Andrew's Ambulance Association.

Such a résumé of his career does little to describe the charm and personality of Professor Lennie, whose popularity as a clinician and teacher was much appreciated by his students and juniors, and whose geniality and integrity gained the respect and affection of his colleagues throughout the kingdom. Apart from his work, he found time to indulge in his favourite recreations of golf, shooting, fishing, and travel, and in all of these he made many friendships which have lasted throughout his life. He had no enemies, and his death is mourned by his many friends.

Throughout his career Professor Lennie was encouraged and loyally supported by his wife, who survives him.—W. C. A.

I. D. writes: As one who had the privilege of succeeding Bob Lennie in the Regius chair of midwifery at Glasgow University I am in a better position to appreciate the results of his work rather than the doing. What he sowed others have largely reaped. In the first place his greatest achievement was the harmony which he brought to the Glasgow school of obstetrics. The rivalries and personal antipathies of years gone by are now a matter of history and amusement to those who no longer have to suffer them, but Lennie by his kindness and geniality won friends everywhere and enemies nowhere. As a general rule it is only possible to hate whom one fears. Nobody feared Lennie, but liked him instead, because he was a modest man who sought not his own.

His long career in obstetrics goes right back to the beginning of the first world war when he first joined the staff of the Glasgow Royal Maternity Hospital, known affectionately as "Rottenrow." He lived through a period when the ravages of rickets made the Glasgow pelvis famous, or rather infamous, and, following in the footsteps of people like Munro Kerr, he acquired a very great experience of contracted pelvis. His attitude towards the younger obstetricians, though always kind, helpful, and courteous, contained a certain amount of bantering disapproval, for he would often refer to them as "membrane-puncturing, episiotomizing radiocaesareanists." He deplored what he felt was the meddlesome midwifery of a younger generation with its rush to surgical induction and caesarean section as a means of escape from clinical difficulties. He certainly practised what he preached and showed a sang-froid which many must have envied.

With his appointment to the department of gynaecology at the Western Infirmary in Glasgow he had perforce to sever a very long connexion with the Victoria Infirmary, on which much of his practice must have been based; but in doing so he brought together the three Regius clinical chairs under the one roof in the Western Infirmary, and,

furthermore, helped to prepare the way for the much enlarged department of gynaecology which now exists there, but from which he never had any benefit before he retired in 1954.

He was one of the men who helped greatly to establish the cordial and happy relations which now exist between the two rival obstetric schools of Edinburgh and Glasgow, and perhaps unconsciously, but nevertheless as a result of the qualities of his own personality, he did much to make the paths of his successor straight.

Having retired, he never once interfered with the running of the departments which he left, even so much as by comment in conversation, and his behaviour in retirement was a model to all those who have not the modesty to recognize that all of us in turn "are as grass which to-day is and to-morrow is cast into the oven."

CHARLES EDWARDS, M.D.

Dr. Charles Edwards, who was in general practice for many years, first at Bridport, Dorset, and, later, at Andover, Hampshire, died at his home at Bournemouth on February 15. He was 85 years of age.

Charles Edwards was born at Blackheath, London, on July 6, 1875. After qualifying from Guy's Hospital in 1900 he held the appointments of assistant medical officer at Peckham House, London, and assistant medical officer and pathologist at the City of London Asylum, Dartford. About 1906 he settled in general practice at Bridport, where he became also surgeon to the local hospital. Later appointments included those of oculist to the Dorset education committee and medical officer to the Bridport, Beaminster, and Lyme Regis Isolation Hospital. In the early days of the first world war he was a civil medical examiner of Army recruits, later serving in the R.A.M.C. with the 2nd Bedfordshire Regiment. After the war he became honorary medical officer to the Edith Cavell Home at Bridport. He was an honorary life member of the St. John Ambulance Association. In 1920 he was granted the M.D. by Durham University, and in the same year was appointed a justice of the peace for Bridport.

Dr. Edwards left Bridport in 1921 to take up another practice at Andover, where he was also medical officer to the hospital, and quickly identified himself with the civic life of the town, becoming mayor of the borough in 1927. A member of the British Medical Association for nearly 60 years, he was chairman of the Winchester Division in 1929–30. He retired from practice in 1935, and went to live at Bournemouth. He leaves a widow.

W. DE LACEY, M.R.C.S., L.R.C.P.

Dr. William De Lacey, who practised in Swindon for 27 years, died on February 23, at the age of 56.

William De Lacey was born in Merthyr Tydfil and qualified at the London Hospital in 1931. He held house appointments at hospitals in Eastbourne and Southend and was the first house-physician to be appointed to the new Southend General Hospital. For the last 27 years he had practised in Swindon. During the second world war he was appointed honorary anaesthetist to the Victoria Hospital, Swindon, and in 1948 he became S.H.M.O. in anaesthetics to the Swindon and Cirencester hospital groups.

Dr. De Lacey married Stella Kehoe in 1934, and she and their four children survive him.

J. E. S. writes: The death of "Bill" De Lacey at the age of 56 has come as a shock to us all. We knew him as a modest and retiring person, ever ready to listen to other people's troubles, and to many he was counsellor and guide. He was a well-read man with an excellent command of English. A keen golfer, he would often reveal his great sense of humour during a game of golf. What little spare time he had was given to his family, to whom he was devoted. During the last weeks of his life, when he realized that he would not recover, he displayed remarkable courage and never lost his composure. He preferred even at this stage to listen to the troubles of others rather than discuss his own health.

He leaves a devoted wife, a son, and three daughters, one of whom is a nurse at St. George's Hospital. His many friends and patients will miss him, and he will be a great loss to Swindon.

ARTHUR WRIGHT, M.B., Ch.B.

Dr. Arthur Wright, who practised until recently in Portobello, Edinburgh, died in Edinburgh on February 23, aged 73.

S. J. P. writes: Born in Prestonpans on April 26, 1887, Arthur Wright completed his medical course at the University of Edinburgh in time to go to France in the first world war with the 51st Division. After his war experiences his heart was set on surgery, but eventually he decided to enter general practice. He settled in Portobello, and there he met and married his friendly rival, Dr. Elizabeth Baxendine, this establishing a very happy partnership in every sense of the word.

It is difficult to depict in words the depth of character, the width of human and professional wisdom, and the inexhaustible fund of kindliness which made the man. Quiet himself, he made friends quietly and without haste. It took a little time to break down the barriers of reserve with which he surrounded himself, but, once admitted to the circle of his friends, new facets of his character kept appearing, so that his friendship was a continuous journey of discovery—and how much there was to discover.

His professional life was above reproach. His medical duties included those of medical officer at the Post Office and Treasury, appointed factory doctor, and, by choice, he became very interested in St. Andrew's Ambulance Association both as lecturer and examiner. His private life was enriched by good music, good books, and a love of the country. His interest in music was almost professional, and he became known as an authority on Delius. In the country he was happiest in the Borders and at his favourite hobby of fishing.

He combined to an unusual extent a rather serious outlook on life with a pawky Scottish sense of humour. Almost to the very end the humour showed through the weary hours. Understanding his condition and the prognosis, he showed magnificent courage through almost a year of continuous pain. In this combination of gentleness and courage lay his greatest strength, and those who were privileged to know him—colleagues, patients, friends—will long remember him.

E. F. L. writes: I wish to add my tribute to my late chief, Dr. Arthur Wright, for to him and to his wife I owe much. Dr. Wright was always a great tower of strength. His teaching was unobtrusive and willingly given at all times, his clinical judgment astute, his surgical skill great, and his faithful, loyal, and devoted care of patients unsurpassed—an example to all. He gave of himself freely, drawing on his unique gift of humour, his common-sense approach to problems, his courage in the face of any adversity, his compassion for human frailties, and his very deep and precious philosophy of life. His patients grieve the loss of their dearly beloved physician, whom they have so missed since his recent retirement. We extend our deep sympathy to his devoted wife and the members of his family.

J. J. McCANN, M.B., B.S., M.R.C.P.

Dr. J. J. McCann, physician superintendent of Pinewood Hospital, Wokingham, Berkshire, died at Pinewood on March 9 at the early age of 51 years.

John Joseph McCann was born on September 21, 1909, the son of Dr. Michael McCann, a family doctor of the old school, who formerly practised in South-west London and who died only last September. After leaving Wimbledon

College he went to St. Thomas's Hospital, where he qualified M.R.C.S., L.R.C.P. (London) in 1932, subsequently taking the M.B., B.S. (London) in 1935 and the M.R.C.P. in 1938. After holding house appointments at St. Thomas's Hospital he joined the London County Council medical service as a general physician and worked at St. Giles's, St. Peter's, and Hackney Hospitals until 1942, when he joined the R.A.M.C. His Army service was interrupted in 1943 when he was found to be suffering from the first of the serious illnesses which were to dog his life and of which he made so light. After his recovery he joined the staff of Pinewood Hospital, then an L.C.C. sanatorium, where he continued to work until his death, having been appointed physician superintendent in 1951. Besides medicine he had wide interests in and around Crowthorne: he was a member of the parish council, of the board of the Wokingham United Charities, and a governor of Easthampstead Park College and Edgbarrow Secondary School.

John McCann had a true zest for life, and lived, in his all-too-few years, the full life. As a doctor he was most painstaking and thorough, and was in his element in the solution of some obscure medical problem: in debates and discussions with colleagues he was a formidable opponent and argued his case with wit and ability. As physician superintendent he had to undertake a certain amount of administration, a task of which he was never fond, but carried out with his usual good humour: of his administrative duties he enjoyed most his work with the British Student Tuberculosis Foundation. To the students, to whom he was known as "The Dean" from the inception of the unit, he was their doctor, friend, and counsellor. Committee work he hated: he often said that the only essential qualification for membership of a hospital committee was unsuitability for any other form of paid or unpaid work.

As a Christian, in the true sense of the word, he ministered to all his patients and friends of whatever colour, creed, or sect. He was consultant and adviser to many in trouble and the friend of all. He regarded and often spoke of those who were privileged to work with him as members of one family, and this attitude has maintained a unity and comradeship in the hospital which is rarely seen.

To his widow Joan and six young children we extend our deep sympathy.—A. J. M.

P. E. B. writes: John McCann was a shining example of a true physician: by his great understanding of human nature and real love of people he was able to give to each of his patients wisdom and understanding of the highest order. His career as a general physician was curtailed by illness and led him to work at Pinewood when it was a tuberculosis sanatorium. He never, however, allowed this to narrow his interests, and he was therefore able to bring a prepared and well-informed mind to deal highly efficiently with the many problems of chest diseases when Pinewood, in recent years, enlarged its scope. During his time as medical superintendent he took the closest possible interest in the lives of every member of the medical, nursing, and lay staff, so that with his passing each one feels that he has lost a personal friend. A man of strong religious conviction, he was also one who entered into a wide variety of life's activities with enthusiasm and zest—and he had an extremely happy family life.

C. A. J. writes: With the death of John McCann, Pinewood Hospital has lost a great deal more than a physician superintendent; for the many hundreds of patients, for the staff and his colleagues, this man was the symbol and the fact, a great doctor. John McCann possessed all the qualities needful to become the family practitioner of the best tradition, and these he poured out unstintingly in his daily life, giving to the hospital the warm atmosphere of a home. Here was a man with whom you could discuss your family and its problems, obtain help over anxieties at work, or talk enthusiastically about cricket—and get back your health. It was because of these especial characteristics that the Students' Tuberculosis Unit which John McCann founded and ran proved such a remarkable success. Here gathered together into the Pinewood huts students of all nationalities and faculties stricken with tuberculosis at a critical period of their studies. Here they worked, had their treatment, were tutored, took their examinations, and found their guide, philosopher, and friend in the doctor who shared their jokes, their problems, and their beer.

Everybody in the local community was known to John. His humanity and deep, warm fellowship gave to the old Cockneys with their emphysematous lungs in the bronchitis unit a comrade's trust of one who knew London as well as they. The young girls with tuberculosis discovered comfort and confidence in this man who became their "father," while those who worked with him found a sound medical judgment and a critical mind both stimulating and provocative. To his dear bereaved wife and family, who so generously shared their John with his other family outside, we who knew him say, "Thank you."

J. M. COWIE, M.D., D.P.H.

Dr. J. M. Cowie, who was medical officer of health for Burton-on-Trent for 37 years, died at his home there on March 9. He was 85 years of age.

James Macrae Cowie was born in Aberdeenshire on September 16, 1875, and was a medical student at Aberdeen University, where he graduated M.B., Ch.B. in 1898, being awarded the Matthews Duncan gold medal in midwifery. He proceeded to the M.D., with honours, in 1903. After graduation he spent a period in general practice, and then took the Aberdeen D.P.H. in 1900. Soon afterwards he was appointed assistant medical officer of health for the City of Manchester, later becoming senior assistant, and for a time he was resident medical officer at the Clayton Vale Isolation Hospital, Manchester. In 1904 he was appointed medical officer of health for Burton-on-Trent and superintendent of the infectious diseases hospital. To these duties were later added those of school medical officer and chief tuberculosis officer. He retired from these appointments in 1941.

A member of the British Medical Association for nearly 60 years, he was a past-president of the Midland branch of the Society of Medical Officers of Health. Before the onset of persistent illness some four years ago he was a remarkably active man, being able to enjoy a round of golf until he was in his eighties. A keen member of the Presbyterian church, he was the chairman of the management board of his church in Burton for 30 years. He leaves a widow.

R. M. HILEY, M.R.C.S., L.R.C.P.

Dr. R. M. Hiley, formerly tuberculosis officer in the Pontypridd and Rhondda area of South Wales and later consultant chest physician under the Welsh Regional Hospital Board, died suddenly on March 12 at the age of 77.

Reginald Melville Hiley was born on November 8, 1883, and educated at King's College, Taunton, Bristol University, and King's College Hospital. Qualifying in 1910, he held several posts as house-physician and then decided to specialize in tuberculosis. His was one of the first appointments made to the King Edward VII Welsh National Memorial Association, for in 1912 he was assigned to the Pontypridd and Rhondda area as tuberculosis officer. There his outstanding ability as a general clinician enabled him to derive full satisfaction from the rich variety of the material referred to his clinic. On the introduction of the National Health Service he became a consultant chest physician. He retired at the end of 1948. His professional life thus covered the entire range of treatment of tuberculosis, from the simple days of the rest and fresh air regimen through tuberculin and gold injections, collapse therapy, and thoracic surgery to the present era of antibiotics.

In local B.M.A. affairs he gave valuable assistance for many years. He was chairman of the North Glamorgan and Brecon Division in 1931–2, and later was honorary secretary of the Division and of the South Wales and Monmouthshire Branch. A member of the Welsh Committee from 1934 to 1937, he also served on the Charities Committee and as a representative at several Annual Meetings.

A keen sportsman, he was chief medical officer to the Welsh Amateur Boxing Association and an administrative steward of the British Boxing Board of Control for many years. Well-grounded in the classics, he read widely, thus adding zest to his natural talent as a conversationalist. He was a most entertaining companion. His kindness and broad humanity endeared him to his patients, to his colleagues, and, not least, to the many past graduates who had the gift of his wise guidance. In his retirement he lived at Tunbridge Wells.

Dr. Hiley leaves a daughter, to whom goes the sympathy of his many friends.—J. F. H.

J. DOUGLAS ROBERTSON, M.D., Ph.D., D.Sc. F.R.C.P.

Dr. J. Douglas Robertson, consultant in chemical pathology at the West London Hospital, died at his home in Harley Street on March 14. He was 57 years of age.

John Douglas Robertson, who was born in Arbroath, Scotland, on June 30, 1903, was the son of Alexander Maclaren Robertson, magistrate and provost of Arbroath. He graduated M.B., Ch.B., with distinction in chemistry, at St. Andrews in 1926. In his student days, and later, he was a great games player, representing his university at rugby, hockey, and cricket. Later he acquired renown as a competitive squash player. In 1929 he took the D.P.H., and in the following year he proceeded M.D., with honours and gold medal.

In the year that the Courtauld Institute was founded at the Middlesex Hospital Dr. Robertson was appointed assistant biochemist there, remaining in that post for nearly 20 years. For the greater part of this time he was in charge of the clinical section of the institute. Being excellent with patients, he was regarded by many of those with chronic disorders, such as diabetes, as a great personal friend and influence in their lives.

As a research worker he would become interested in a particular subject and then devote himself to it with fanatical zeal, working all hours of the day and night. His great interest was the determination and investigation of the basal metabolic rate in human beings. He probably knew as much on this subject as anybody in Britain. The series of British standards he built up are much more satisfactory than those in use when he began his work on basal metabolism. Another of his experimental interests was intraocular tension, and he published a series of important papers on the mechanism of the maintenance of the tension. A great self-experimenter, he was attracted to all kinds of strange diets, and he also succeeded in burning himself to a deep mahogany colour by exposing himself to ultra-violet light.

During his years at the Courtauld Institute he extended the scope of his academic achievements, taking the M.R.C.P. in 1938 and graduating D.Sc. at St. Andrews and Ph.D. at London. A Territorial, he served as a captain in the R.A.M.C., being attached to the Scottish Horse, and after the war he visited the United States as Mayo Foundation Lecturer and as Alpha Omega Alpha Lecturer at Wayne University, Michigan. Elected F.R.C.P. in 1946, he joined the staff of the London Clinic as director of the department of clinical investigation. Some years later he became consulting chemical pathologist at the West London Hospital. He was also consulting pathologist to British European Airways and honorary secretary of the Research Defence Society. In the latter capacity he did much good work. When he took on the post in 1947 the Society was at its lowest ebb, and it was due to Robertson's efforts that the decline was reversed and that the Society has been slowly but steadily gaining ground ever since. He changed the name of its journal from *The Fight Against Disease* to *Conquest*, and collected enough authoritative articles on the contribution of animal experiments to medicine to publish *Conquest* four times a year. He also arranged for the publication of the first edition of *Notes on the Law Relating to Animal Experiments in Great Britain*.

Dr. Douglas Robertson was greatly respected by his colleagues and always very helpful to those in any difficulty. He leaves a widow and stepson.

LLEWELYN REES, M.R.C.S., L.R.C.P.

Dr. Llewelyn Rees, who had practised in Cardiff for nearly thirty years, died in hospital on March 22. He was 55 years of age.

Llewelyn Rees was the younger son of the late Dr. John Morgan Rees, of Pontypridd. Born on May 4, 1905, he was educated at King's School, Worcester, the Cardiff Medical School, and St. Thomas's Hospital, qualifying in 1931. After holding the posts of house-surgeon and casualty officer at Cardiff Royal Infirmary he went into practice in Cardiff, where he remained for the rest of his life.

J. W. T. T. writes: Dr. Llewelyn Rees had suffered from serious illnesses in the past few years, but in spite of this had maintained a cheerful outlook with great courage and fortitude. He came of a medical family. His brother, Dr. Teddy Rees, who died last August, was in practice in Pontypridd, where their father had practised for many years. All three doctors took an active interest in B.M.A. affairs and held office in responsible positions. Between the two brothers there was a strong affection, and in the B.M.A. they found a great deal of common interest. Dr. Llewelyn Rees was honorary secretary of the Cardiff Division of the B.M.A. for seven years, and was a devoted and valuable member of committees.

By his earnest and friendly nature he earned the esteem and high regard of his colleagues in South Wales and of a large circle of friends. He was known to his friends as "Bonzo," and somehow this seemed to indicate the geniality of spirit which was his. His cheerful presence at many of our functions will be sadly missed, and so will his valuable help, so readily given, at B.M.A. meetings. It can indeed be truly said of him that he was dearly beloved by all who knew him. He leaves a widow, a son, who is a student at St. Thomas's, and two daughters, to all of whom we extend our deep sympathy.

A friend writes: The medical background to his early life, and the closely knit family of which he was a part, gave something to Llewelyn Rees which was to stand him in good stead. His student friends realized from the start that he was going to be a good doctor, though, unfashionably, he tended to be as much interested in patients as in their diseases. Consequently, even as a young man he had an unusual understanding of human foibles. And as a friend he had all the prime virtues—loyalty, steadfastness, cheerfulness, and tolerance. The news of his death has brought sadness to many.

The winter number of the *N.O.T.B.A. Bulletin*, issued by the National Ophthalmic Treatment Board, appears with a cover for the first time. The chairman, Dr. R. W. STEPHENSON, takes the opportunity in an introductory letter to reaffirm the main object of the N.O.T.B.A.—namely, to facilitate a medical eye examination for the general public.

Medico-Legal

BLINDNESS NOT AN ILLNESS

[FROM OUR LEGAL CORRESPONDENT]

In a recent rating appeal heard in the Court of Appeal[1] Lord Evershed, the Master of the Rolls, said that blindness is not an illness within the meaning of section 28 (1) of the National Health Service Act. Section 28 (1) provides as follows:

> "A local health authority may with the approval of the Minister, and to such an extent as the Minister may direct, shall make arrangements for the purpose of the prevention of illness, the care of persons suffering from illness or mental defectiveness, or the aftercare of such persons. . . ."

The definition section of the Act (section 79 (1)) provides that for the purpose of the Act: "Illness includes mental illness and any injury or disability requiring medical or dental treatment or nursing."

It follows from Lord Evershed's statement of the law that any expenditure by a local authority in providing, for instance, a home for blind people would be an expenditure *ultra vires* the powers conferred by section 28 (1). The local authority could make such expenditure only if authorized by some other statutory provision.

If the legality of such expenditure were questioned before a court, Lord Evershed's opinion on this point might be distinguished. Of the two other judges of the Court of Appeal, Lord Justice Pearce said it was "at least open to doubt" whether blindness was an illness within the meaning of section 28 (1) (and he decided the point on other grounds), and Lord Justice Harman expressed general agreement with the other members of the court.

Leave to appeal to the House of Lords has been granted, and the question of an appeal is being considered.

[1] (1961) 1 WLR 24.

Universities and Colleges

UNIVERSITY OF OXFORD

The following have been reappointed university lecturers from October 1, 1961, to September 30, 1966, in the subjects indicated in parentheses: Dr. A. M. Cooke, Dr. P. C. Mallam, and Dr. E. M. Buzzard (Medicine); Mr. D. C. Corry, Mr. A. Elliot Smith, and Mr. J. C. Scott (Surgery); Dr. F. H. Kemp (Radiology); Sir William P. Macarthur (Tropical Medicine); Mr. R. G. Macbeth (Otolaryngology); Dr. W. Ritchie Russell (Neurology); Dr. Victoria Smallpeice (Diseases of Children); Mr. J. A. Stallworthy (Obstetrics and Gynaecology); Mr. J. B. Pennybacker (Neurosurgery).

The following have been reappointed clinical lecturers from October 1, 1961, to September 30, 1966, in the subjects indicated in parentheses: Mr. R. G. Taylor and Mr. G. E. Maloney (Surgery); Mr. W. S. Lewin (Neurosurgery); Dr. A. F. Alsop, Dr. F. K. Boston, and Dr. J. V. Mitchell (Anaesthetics); Dr. F. Ridehalgh (Chest Diseases); Dr. J. Badenoch (Medicine); Dr. J. F. Warin (Infectious Diseases); Dr. C. W. M. Whitty (Neurology); Mr. W. Hawksworth (Obstetrics and Gynaecology); Mr. J. P. F. Lloyd (Ophthalmology); Mr. G. H. Livingstone (Otolaryngology); Dr. H. L. Ellis (Paediatrics); Dr. F. Ellis (Radiotherapy); Mr. G. C. L. Pile (Thoracic Surgery).

UNIVERSITY OF CAMBRIDGE

Dr. D'A. Kok has been reappointed a University Lecturer in the Department of Medicine with tenure from October 1, 1961, to the retiring age.

In Congregation on February 25 the degrees of M.B., B.Chir. were conferred by proxy on G. D. Ingram.

Dr. H. B. Barlow has been reappointed an Assistant Director of Research in the Department of Physiology with tenure from October 1, 1961, for five years.

The following reappointments are announced: Dr. C. W. McE. Pratt, as University Lecturer in the Department of Anatomy, and Dr. G. A. Gresham and Dr. A. P. Waterson, as University Lecturers in the Department of Pathology, all with tenure from October 1, 1961, to the retiring age. Dr. T. D. Kellaway has been reappointed University Demonstrator in the Department of Pathology, with tenure from October 1, 1961, for two years.

In Congregation on March 11 the degree of M.B. was conferred on Mrs. Wendy D. Savage (by proxy) and J. R. Parker.

UNIVERSITY OF ABERDEEN

At a Graduation ceremony to be held on July 7, the honorary degree of LL.D. will be conferred on George Swapp, D.C.M., M.M., M.B., Ch.B., a general practitioner in Aberdeen.

Dr. K. D. Sargison resigned from a terminable Lectureship in Anatomy on March 31.

Dr. Alexander C. Turnbull has been appointed to a Senior Lectureship in the Department of Midwifery and Gynaecology from July 1, 1961.

UNIVERSITY OF EDINBURGH

The honorary degree of LL.D. will be conferred on Sir Frederic Bartlett, F.R.S., professor emeritus of psychology in the University of Cambridge, and Professor John McMichael, F.R.S., professor of medicine in the University of London, at a graduation ceremonial to be held on July 7.

At a meeting of the University Court held on February 20 Dr. M. H. Draper, senior lecturer in physiology, and Dr. E. B. French, senior lecturer in medicine, were admitted to membership of the Faculty of Medicine.

Dr. I. S. McRobbie has submitted his resignation from the appointment of Lecturer in the General Practice Teaching Unit, as from July 31, 1961.

Dr. George Dick, formerly medical officer of health for the County of Caithness, has bequeathed to the University £2,000, the income therefrom to be used to provide a prize to be known as the William and Isabella Dick Prize, in memory of his parents and of his daughter.

Dr. Dugald L. Gardner has been appointed Senior Lecturer in Pathology.

Dr. G. Monaghan, Assistant in the Department of Pathology, has submitted his resignation, as from July 31, 1961.

UNIVERSITY OF LONDON

Dr. D. W. Parsons, who was awarded the John Marshall Fellowship in Surgical Pathology for two years from November 1, 1959, resigned the Fellowship as from December 31, 1960. The Fellowship has been awarded for two years from January 1, 1961, to Mr. J. C. Smith, who will also hold the Whait Fellowship awarded by University College Hospital Medical School.

The title of Professor of Orthodontics in the University has been conferred on Dr. D. P. Walther, in respect of his post at the Royal Dental Hospital of London School of Dental Surgery.

The title of Reader in Chemical Pathology in the University has been conferred on Dr. I. D. P. Wootton in respect of his post at the Postgraduate Medical School of London.

On February 22 the degree of M.D. was awarded by the Senate to J. K. Wing.

Professor Mary Lucas Keene has been nominated for appointment as a representative of the University on the governing body of the Dartford College of Physical Education, and Dr. C. F. Harris for reappointment on the council of the Royal College of Veterinary Surgeons.

The following have been recognized as teachers of the University in the subjects indicated in parentheses: *London School of Hygiene and Tropical Medicine* and *Guy's Hospital Medical School*, Dr. R. M. Acheson (Medicine). *Westminster Medical School*, Dr. H. M. T. Coles (Children's Diseases). *St. Thomas's Hospital Medical School*, Dr. Brian Creamer (Medicine), Mr. Philip Rhodes (Obstetrics and Gynaecology), Dr. R. B. Wright (Anaesthetics), and Dr. M. J. Allwood (Physiology). *Institute of Ophthalmology*, Mr. J. R. Hudson and Mr. K. C. Wybar (Ophthalmology). *Guy's Hospital Medical School*, Mr. C. H. Kinder (Surgery). *Postgraduate Medical School of London*, Dr. J. W. Laws (Radiology). *London School of Hygiene and Tropical Medicine*, Dr. C. E. G. Smith (Pathology (Bacteriology)). *Middlesex Hospital Medical School*, Dr. Helen N. Duke (Physiology).

The Mary Scharlieb Research Studentship for 1961–2 has been awarded to Dr. K. A. Porter, to whom it was first awarded for 1960–1.

UNIVERSITY OF MANCHESTER

The following candidates have been approved at the examinations indicated:

DIPLOMA IN PSYCHOLOGICAL MEDICINE.—*Part II:* John Fisher, B. A. Lowe, Maria Rogers. *Part I:* C. S. Mellor, D. H. Morgan, W. A. Weston.

UNIVERSITY OF BIRMINGHAM

The title of First Assistant to the Chair of Pathology has been conferred on Dr. D. B. Brewer, Reader in Pathology, and the title of University Clinical Lecturer in Surgery on Mr. K. D. Roberts, Consultant Thoracic Surgeon, United Birmingham Hospitals.

Dr. Phillida A. Sampson has been appointed Research Associate in the Department of Surgery.

The title of Emeritus Professor has been conferred on Henry Percy Gilding, Bowman Professor of Physiology in the University from 1933 to 1960.

The title of University Research Fellow has been conferred upon the following for the period of their stay in the University: Dr. E. G. McQueen, senior lecturer in pharmacology in the University of Otago, who is working on problems connected with renal disease in the Department of Experimental Pathology, and Dr. Nada Kovacic (in the Department of Medicine), who holds a World Health Organization Fellowship.

Dr. P. R. Kemp has been appointed part-time Lecturer in the Department of Paediatrics and Child Health from October 1, 1960.

Mr. G. D. Oates resigned from the appointment of Lecturer in the Department of Surgery on March 31, 1961.

UNIVERSITY OF LIVERPOOL

The following candidates have been approved at the examinations indicated:

DIPLOMA IN RADIOLOGY: *Radiodiagnosis, Part I.*—G. G. Ahmed, N. D. Basu, R. J. Fielding, C. L. Levene, Yvonne A. Roope, J. R. M. Wilson, T. Yi. *Radiotherapy, Part I.*—H. C. Mansharamani, M. K. Mitter, Norma S. Strelitz.

UNIVERSITY OF LEEDS

The following candidates have been approved at the examinations indicated:

M.D.—F. M. Parsons (with distinction).

CH.M.—K. F. Wood.

DIPLOMA IN PUBLIC HEALTH.—P. H. Brewin, Kathleen A. S. Brosnan, A. Elsworth, Marion E. Jepson, G. T. MacCulloch, M. H. Moles, P. O. Nicholas, C. G. Oddy, Elaine M. Osborne, D. B. Reynolds, F. S. Rogers, A. Shaw, R. Stalker, Elizabeth Wales.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College held on March 9, with Sir Arthur Porritt, President, in the chair, a resolution of condolence was passed on the death of Lord Stopford, Honorary Fellow.

Mr. R. L. G. Dawson was appointed as Adviser in Training in Plastic Surgery.

The appointment of Mr. W. A. Lisle Thompson as Robert Jones Travelling Research Fellow was reported.

Mr. A. Lawrence Abel and Mr. C. Naunton Morgan were reappointed as representatives on the Council of the Imperial Cancer Research Fund.

The Hallett Prize was presented to Captain W. C. Moffat, R.A.M.C., of the University of Glasgow, and the Handcock Prize to M. H. Devereux, of Guy's Hospital Medical School.

The thirtieth Macloghlin Scholarship was awarded to R. T. Watson, of Marlborough College.

A Diploma of Membership was granted to E. J. W. Gumpert.

The Council agreed to a request from the Government of Pakistan for a Primary F.R.C.S. examination to be held in Lahore in January, 1962.

After the meeting a Hunterian Lecture was delivered by Professor R. C. Connolly on "Cerebral Ischaemia in Spontaneous Subarachnoid Haemorrhage."

ROYAL COLLEGE OF SURGEONS IN IRELAND

On March 24 the Fellowship in Surgery of the College was conferred on G. M. Irvine (*ad eundem*) and S. M. A. Messieh.

On March 24 the Licence in Surgery and Midwifery of the College was conferred on the following successful candidates: M. J. Cox, Helen A. Fenton, G. R. Gupta, T. J. E. Hynes, J. W. Laing, Olive E. Mullen, K. S. Vig.

UNIVERSITY OF QUEENSLAND

Mr. D. B. Leaming, first assistant in the Department of Surgery, King's College, Newcastle upon Tyne, has been appointed Senior Lecturer in Surgery in the University of Queensland.

Vital Statistics

Influenza

Influenza is the only one of the great epidemic diseases of the nineteenth century that is still a potential large-scale killer in England and Wales. The virus generally undergoes some modification between one outbreak and another, and occasionally a new type arises, such as the Asian strain in 1957. These variations make the future course of influenza quite unpredictable. In the post-war period the mortality from influenza has been low, and even during an outbreak the death rates have been lower than in the non-epidemic years of the 50 preceding years. The general tendency has been for the death rate to continue to decrease. Although the mortality has been low the incidence in recent outbreaks appears to have been high, particularly in closed communities. Antibiotics have probably accelerated the fall in the death rate in recent years, but they cannot be the sole explanation for the fall, since the death rates have declined since 1929.

Influenza generally appears in the community at the turn of the year and is prevalent during the first quarter. The Asian type appeared in the early autumn, and, despite the fears that the outbreak might develop into a pandemic by lasting until the normal influenza period and then flaring up, it died out, with the moderate death rate of 150 per million.

The outbreak in 1961 has differed from the recent outbreaks in two ways: (1) lack of spread, and (2) age of fatal attacks. The present outbreak began in the north-midland counties and spread to the north-western counties of Lancashire and Cheshire and to Yorkshire, but failed to spread to the remainder of the country with the same intensity. During the first eleven weeks of this year 6,245 deaths have been registered: 22.2% were in the north-western counties, 13.1% in Yorkshire, 21.3% in the north-midland counties of Derby, Lincs, Notts, Staffs, and Warwickshire. The four northern counties had only 2.4% of the deaths, Wales 6.8%, and the remainder of the country, the eastern, south-midland, London, and south-east, southern, and western counties 34%.

In the 1957 outbreak a very high incidence among children and young adults was recorded, particularly in closed communities, and, although the case fatality was low, the death rate at ages under 44 years was the highest in the post-war period. In the first eleven weeks of the present outbreak 4.8% of the deaths were among those aged 0–44, and 77.3% among those aged 65 years and over, compared with 18.1% at ages 0–44 in 1957 and 52.6% at ages 65 and over.

Road Accidents in January

In January, 1961, 552 people died as a result of road accidents, 45 more than in January, 1960; 35 were children, an increase of 4% over the previous year. The largest increase in deaths was among pedestrians, 39 more than in January last year.

Infectious Diseases

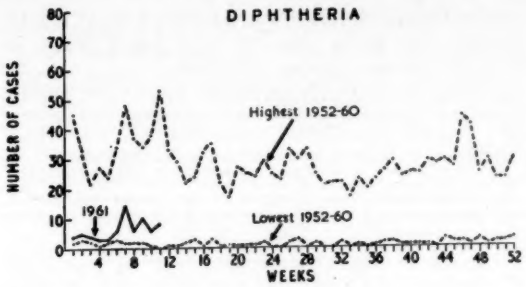
Areas where the numbers of notifications were high in the latest two weeks for which figures are available.

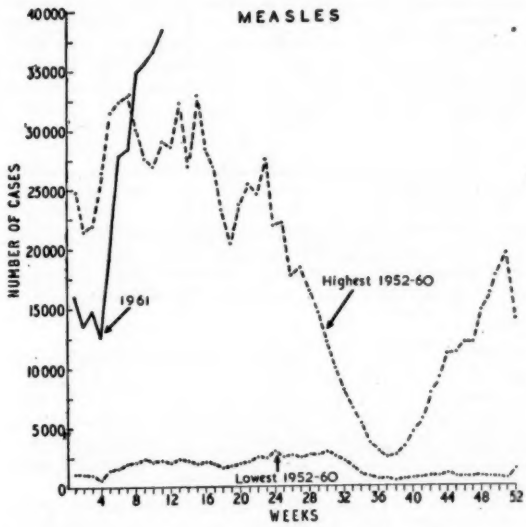
Measles	Week Ending Mar. 11	Mar. 18
Durham	1,962	**1,766**
Sunderland C.B.	436	**363**
Essex	2,547	**2,798**
West Ham C.B.	214	**307**
Chelmsford M.B.	176	**187**
Ilford M.B.	212	**151**
Romford M.B.	192	**261**
Gloucestershire	380	**478**
Bristol C.B.	215	**207**
Hampshire	1,570	**1,582**
Southampton C.B.	296	**413**
Havant and Waterloo U.D.	281	**178**

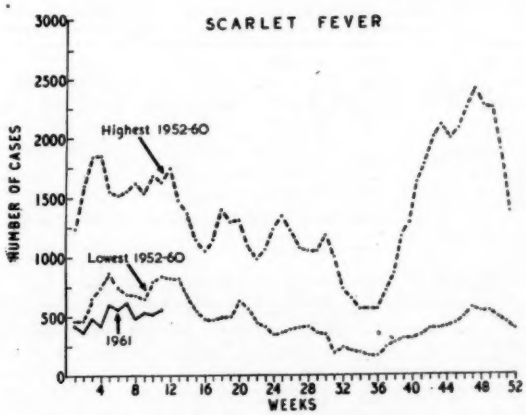
Herefordshire	192	**252**
Hereford M.B.	110	**123**
Kent	1,827	**2,013**
Chislehurst and Sidcup U.D. ...	163	**198**
Lancashire	2,223	**2,225**
Manchester C.B.	300	**297**
Lincolnshire	799	**753**
Grimsby C.B.	119	**220**
London	2,986	**3,032**
Lambeth	213	**269**
Lewisham	272	**293**
Wandsworth	341	**323**
Woolwich	220	**222**
Middlesex	1,946	**2,467**
Harrow M.B.	226	**256**
Hendon M.B.	154	**232**
Willesden M.B.	221	**188**
Northamptonshire	258	**257**
Northampton C.B.	182	**205**
Northumberland	568	**623**
Newcastle upon Tyne C.B.	224	**283**
Nottinghamshire	691	**645**
Nottingham C.B.	265	**266**
Staffordshire	1,442	**1,530**
Walsall C.B.	143	**278**
Surrey	1,214	**1,452**
Croydon C.B.	215	**281**
Warwickshire	2,749	**3,181**
Birmingham C.B.	1,364	**1,561**
Coventry C.B.	577	**673**
Solihull M.B.	249	**236**
Wiltshire	402	**455**
Swindon M.B.	280	**302**
Yorkshire East Riding	767	**804**
Kingston upon Hull C.B.	573	**542**
Yorkshire West Riding	2,448	**2,387**
Leeds C.B.	255	**226**
Sheffield C.B.	375	**339**
Glamorganshire	1,110	**1,174**
Cardiff C.B.	410	**552**
Dysentery		
Essex	57	**74**
Chigwell U.D.	9	**24**
Dunmow R.D.	16	**16**
Lancashire	67	**95**
Liverpool C.B.	5	**14**
Eccles M.B.	11	**18**
Leicestershire	12	**29**
Leicester C.B.	12	**27**
London	52	**82**
Islington	17	**42**
Yorkshire West Riding	210	**236**
Bradford C.B.	38	**27**
Huddersfield C.B.	14	**44**
Leeds C.B.	57	**52**
York C.B.	52	**24**
Thorne R.D.	5	**23**
Diphtheria		
London	1	**3**
Camberwell	0	**2**
Warwickshire	4	**5**
Birmingham C.B.	4	**5**

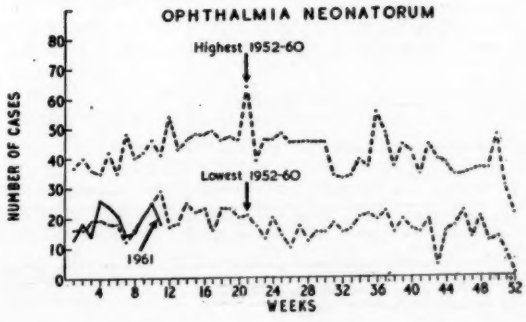
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1952–60 are shown thus ------, the figures for 1961 thus ———. Except for the curves showing notifications in 1961, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **March 18** (No. 11) and corresponding week 1960.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	8	3	0	0		0	0	2	0	1
Dysentery ..	761	82	108	13	4	1,874	192	236	32	7
Encephalitis, acute	1	0		0		4	0	0	0	
Enteric fever:										
Typhoid ..	2	0	0	1		1	0	0	0	
Paratyphoid ..	3	0	6(B)	0		1	0	0	0	2
Food-poisoning ..	124	21	8	0		174	24	7	0	
Infective enteritis or diarrhoea under 2 years				8	20				12	21
Measles*	38,485	3032	822	466	410	2,247	100	64	6	90
Meningococcal infection	24	0	9	0		23	2	9	0	
Ophthalmia neonatorum	18	2	3	0		31	4	6	0	
Pneumonia† ..	389	28	216	1	9	414	19	210	9	2
Poliomyelitis, acute:										
Paralytic ..	1	0	0	0	1	4	0	0	0	
Non-paralytic ..	4	0	1			4	0	0		
Puerperal fever‡ ..	180	27	10	1		166	19	11	0	
Scarlet fever ..	552	38	35	30	17	1,176	50	82	24	12
Tuberculosis:										
Respiratory ..	426	32	40	22		469	59	68	16	
Non-respiratory	57	3	1	3		69	6	6	3	
Whooping-cough	864	41	63	9	30	896	72	193	3	30

DEATHS	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	0	0	0	0	0	0
Dysentery ..	1	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever ..	1	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	14	0	3	0	0	9	0	2	0	0
Influenza	104	1	6	3	1	33	0	0	0	1
Measles		0	1	0	0	0	0	0	0	0
Meningococcal infection		0	1				0	0		
Pneumonia ..	680	44	31	26	7	734	63	14	17	7
Poliomyelitis, acute	0	0		0	0	1	0		0	0
Scarlet fever ..		0	0	0	0	0	0	0	0	0
Tuberculosis:										
Respiratory ..	74	5	7	0	2	75	4	9	0	5
Non-respiratory		1		0	0		2	0	1	0
Whooping-cough	1	0	0	0	1	0	0	0	0	0
Deaths 0–1 year ..	367	36	26	14	14	347	29	32	10	9
Deaths (excluding stillbirths) ..	10,890	832	605	134	151	11,242	864	603	140	170
LIVE BIRTHS ..	16,656	1390	1026	230	419	16,115	1366	1031	216	371
STILLBIRTHS ..	349	34	29			333	33	23		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
‡ Includes puerperal pyrexia.

Medical News

General Medical Council Elections

Eleven candidates were nominated for the eleven places in the General Medical Council for the next term of office, and the following candidates were accordingly elected for the period of five years from April 30 by the fully registered medical practitioners resident in (1) *England and Wales*: Dr. G. O. BARBER, Mr. L. DOUGAL CALLANDER, Dr. W. V. HOWELLS (resident in Wales), Dr. A. TALBOT ROGERS, Dr. S. NOY SCOTT, Dr. S. WAND, Mr. WELDON P. T. WATTS, Dr. K. G. LLOYD WILLIAMS; (2) *Scotland*: Dr. I. D. GRANT, Dr. G. W. IRELAND; (3) *Ireland*: Mr. W. DOOLIN.

Vice-chancellor of Madras University

Sir ARCOT MUDALIAR, Vice-chancellor of Madras University and chairman of this year's World Health Assembly,

The Vice-chancellor of Madras University makes a presentation to the Queen.

is shown here presenting a casket to H.M. QUEEN ELIZABETH on the occasion of her visit to the university during her tour of India. Sir Arcot graduated in medicine from the Medical College, Madras, and holds, in addition to his many other distinctions, the Fellowship of the Royal College of Obstetricians and Gynaecologists.

The Hippocratic Oath

From time to time the Public Relations Department of the B.M.A. receives inquiries from newspapers and members of the public about the form of Hippocratic Oath believed to be taken by doctors at graduation ceremonies. In order to obtain information about this the Public Relations Department asked the deans of all the 31 medical schools in the United Kingdom if the Hippocratic Oath was sworn by doctors graduating at their universities. The inquiry disclosed that a special ceremony at which an oath or pledge or *Sponsio Academica* was taken was held at six universities: Edinburgh, Glasgow, St. Andrews, Aberdeen, Belfast, and the University of Wales (Welsh National School of Medicine). At the other 25 medical schools there was no official ceremony at which an oath was sworn. Further details can be obtained from the Chief Press Officer, B.M.A. House, Tavistock Square, London W.C.1.

"La Presse Médicale" Film Prize

The annual prize given by *La Presse Médicale* for the best foreign film in the medical or surgical field has recently been awarded in Paris to "The Story of Oxytocin" made under the direction of Professor W. C. W. NIXON, of University College Hospital, in collaboration with Dr. C. N. SMYTH and Dr. G. W. THEOBALD, and with the co-operation of the Sandoz Laboratories. The film outlines the history, chemistry, pharmacology, and clinical applications of oxytocin in obstetrical practice.

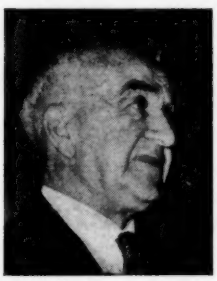
Samson Gemmell Chair of Child Health, Glasgow University

Dr. J. H. HUTCHISON, Leonard Gow lecturer in the diseases of infancy and childhood in the University of Glasgow and visiting physician in charge of wards at the Royal Hospital for Sick Children, Glasgow, has been appointed to the Samson Gemmell Chair of Child Health, Glasgow University, from October 1, when the present occupant, Professor STANLEY GRAHAM, retires.

Dr. Hutchison was educated at the High School of Glasgow and Glasgow University. He graduated in medicine and surgery in 1934 and took his M.D. in 1939. He is a Fellow of the Royal Faculty of Physicians and Surgeons of Glasgow (1937), of the Royal College of Physicians of London (1947), and of the Royal College of Physicians of Edinburgh (1957). He held hospital appointments in the Royal Hospital for Sick Children, Glasgow, the Western Infirmary, Glasgow, and St. Luke's Hospital, Bradford, before being called from the Reserve on the outbreak of war in 1939. He served with the R.A.M.C. until 1945, and was with the Army in France and later in North Africa, Italy, and Austria. In 1945 he was awarded the O.B.E. He has held his present appointments since 1947, as well as appointments as assistant physician for infant ailments, Royal Maternity Hospital, Glasgow, and consultant paediatrician to the Glasgow Eye Infirmary. Dr. Hutchison has carried out investigations into the iron metabolism of children in health and disease, collapse of the lung in children, and cretinism, juvenile myxoedema, and sporadic goitre, on which subjects he has contributed to textbooks and has written numerous papers.

Sir Zachary Cope's Eightieth Birthday

The current issue of *St. Mary's Hospital Gazette* gives an account of the luncheon given in honour of Sir ZACHARY COPE'S eightieth birthday by St. Mary's Medical School and Hospital on February 14. Very warm good wishes for a continued happy and active life were given to Sir Zachary by those who attended. A display of his books and papers was also mounted in the Library, and was greatly appreciated. Sir Zachary gave an address to what was possibly one of the largest congregations the Wright-Fleming Theatre has ever seen, about the people he had known and worked with in the course of his long association with St. Mary's Hospital. He concluded, characteristically, in verse:



> "Scarcely a basic science not advanced
> Scarcely a branch of medicine not enhanced
> By men who in the past have trod these halls,
> Whose voices echo from these very walls
> For you the future years are kept in store—
> Follow the path of those who went before.
> Then you young men, I think, nay, I believe,
> Will just as much, or maybe more, achieve."

"Human Relations in Obstetrics"

The Minister of Health's Standing Maternity and Midwifery Advisory Committee concludes, in its report *Human Relations in Obstetrics*, that there is room for improvement in the way in which some mothers are treated during childbirth, both at home and in hospital. Its main suggestions are that something should be done to remedy lack of privacy and long hours of waiting in some antenatal clinics; that women in labour should always be able to feel that kindly help is at hand, and that, at least in the second stage of labour, they should never be left alone; explanations of what is happening should be given both before and during labour; new maternity units should be made as flexible as possible so that consideration can be given to the mother's wishes. The report's final comment is that if senior staff have a kind, understanding, and tolerant approach to the patient this will be reflected throughout the unit. The Minister of Health has asked authorities with maternity units or departments to report to him by July 31 about what action they have taken on the report's recommendations. (Central Health Services Council; H.M.S.O., price 6d. net.)

Smallpox Vaccination Requirements of France

W.H.O. has confirmed with the health administration of France that only travellers arriving in France who have been in Madrid during the previous 14 days will be required to present a smallpox vaccination certificate. The current outbreak of smallpox in Madrid was started by an air traveller who arrived there from Bombay on January 27; 13 people in the Spanish capital have had smallpox, and three more have died from the disease.

Hunterian Society's Gold Medal Essay Competition

The Gold Medal for 1960 has been awarded to Dr. LOUIS FREEDMAN. The subject for the 1961 essay is "The Management of Diabetes Mellitus in General Practice." The competition is open to all general practitioners resident within the British Commonwealth. Details may be obtained from the Hon. Secretary, Dr. O. GARROD, 31 Weymouth Street, London W.1.

New Name for Enrolled Nurses

Enrolled assistant nurses will be known as enrolled nurses from the end of June. Those who take the two-year practical course for admission to the Roll will be entitled to use the letters S.E.N. (State-enrolled nurse) from the same date.

Grants, Gifts, and Bequests

The Royal College of Obstetricians and Gynaecologists has received a further grant of £6,000 from the Wellcome Trust for library purposes.

The Ford Foundation has made a grant of $500,000 to assist the family planning programme in Pakistan. It will be used for vehicles, audio-visual material, and training fellowships.

The National Fund for Research into Poliomyelitis and Other Crippling Diseases has presented an electron microscope to the Institute of Neurology, National Hospital, Queen Square, for research into muscular dystrophy.

People in the News

Lord ADRIAN is visiting Poland, sponsored by the British Council, at the invitation of the Polish Academy of Sciences.

Mr. B. N. BROOKE, reader in surgery, Birmingham University, has been awarded the Copeman Medal for Scientific Research for 1960 by Corpus Christi College, Cambridge, and he has been invited to give the Sir John Marnoch Memorial Lecture for 1961 at the University of Aberdeen Medical School.

Professor A. C. FRAZER has been appointed the first president of the new British Industrial Biological Research Association.

Professor A. B. MACGREGOR has been nominated as dental health consultant to the Government of Ghana.

Dr. A. SMITHIES (D.Phil.Oxon) has been awarded a Markle Scholarship in Medical Science by the John and Mary Markle Foundation of New York. The University of Wisconsin Medical School will receive $6.000 a year for five years towards supporting his research in medical genetics.

Dr. K. G. BERGIN is to serve for five years as a member of W.H.O.'s Expert Advisory Panel on International Quarantine.

COMING EVENTS

Association of Clinical Biochemists (Southern Region).—Meeting, April 15, Radcliffe Infirmary, Oxford. Details from Mr. G. HIGGINS, Department of Clinical Biochemistry, Radcliffe Infirmary, Oxford.

British Association of Physical Medicine.—Annual meeting, London and Stanmore, April 20. Advanced course, symposium on "Diseases of Muscle" (open to non-members at fee of 21s.), April 21, 22. Details from B.A.P.M., 47 Lincoln's Inn Fields, London W.C.2.

Association for the Study of Medical Education.—Professor J. P. HUBBARD, "Medical Examining in the U.S.A.," April 20. See advertisement p. 54.

Birmingham and Midland Medical Art Society.—Exhibition of paintings, sculpture, lithographs, and pottery by local artists, April 26, 27, 6–10 p.m., Birmingham Medical Institute, 36 Harborne Road, Edgbaston, Birmingham 15.

National Marriage Guidance Council.—Annual conference, "Marriage Guidance at Home and Abroad," May 11–14, Palace Hotel, Buxton, Derbyshire. Details from N.M.G.C., 58 Queen Anne Street, London W.1.

Faculty of Radiologists.—Postgraduate weekend course, "Diagnostic Radiology" and "Radiotherapy," May 13, 14. Details from Secretary of Faculty, 47 Lincoln's Inn Fields, London W.C.2.

Central Sterilizing Club.—Meeting, Bristol, June 26, 27. Details from Dr. J. REVANS, Wessex Regional Hospital Board, Highcroft, Romsey Road, Winchester.

National Association for Maternal and Child Welfare.—Annual Conference, June 28–30, Church House, Westminster, London S.W.1. Opening by Mr. ENOCH POWELL, Minister of Health. Sessions include, "Congenital Malformations," "The Importance of Post-natal Aftercare," "Psychological Aspects of Pregnancy and Labour," "Home or Hospital for Children Who Are Ill," "Co-ordination of the Existing Services for Children," "Prevention of Juvenile Delinquency." Details from Secretary, N.A.M.C.W., Tavistock House North, Tavistock Square, London W.C.1.

Ross Institute of Tropical Hygiene.—Lay course in tropical hygiene designed for planters, mining engineers, and other non-medical people who may be responsible for the health of industrial labour forces in the Tropics. July 3 to 7. Details from Mr. L. G. PONSFORD, Organizing Secretary, Ross Institute of Tropical Hygiene, London School of Hygiene and Tropical Medicine, Keppel Street (Gower Street), London W.C.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, April 10

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Dr. B. G. B. Lucas: Drink, Drugs, and Anaesthesia (illustrated).

Tuesday, April 11

LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., special university lecture in pathology by Dr. Felix Wroblewski (New York): Diagnostic Biochemical Dissection.

MANCHESTER MEDICAL SOCIETY: SECTION OF SURGERY.—At Manchester Victoria Memorial Jewish Hospital, 4 for 4.30 p.m., clinical meeting.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Lumleian Lecture by Professor L. J. Witts: Some Aspects of the Pathology of Anaemia—(1) The Hypochromic Anaemias.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor J. K. Ross: Fate of Autogenous Tissue Grafts in the Heart.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Mr. H. C. Knight: Surgical Treatment of Cervical Spondylosis.

Wednesday, April 12

BIRMINGHAM MEDICAL INSTITUTE: SECTION OF PSYCHIATRY.—At All Saints Hospital, Winson Green, Birmingham, 2.30 p.m., tour of hospital; 4.30 p.m., clinical meeting.

BIRMINGHAM MEDICAL INSTITUTE: MIDLAND MEDICAL SOCIETY SECTION.—At 36 Harborne Road, Edgbaston, 8.30 p.m., annual general meeting. Mr. N. L. Crabtree and Mr. R. S. Strang: Recent Advances in the Treatment of Deafness.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. Harland Rees: Increased Frequency of Micturition.

MANCHESTER MEDICAL SOCIETY: SECTION OF PATHOLOGY.—At Clinical Sciences Building, York Place, 4.30 for 5 p.m., laboratory meeting in the Departments of Pathology and Bacteriology.

NORTH OF ENGLAND COUNCIL OF BRITISH EMPIRE CANCER CAMPAIGN.—At Royal Victoria Infirmary, Newcastle upon Tyne, 5.30 p.m., Emily Blake Memorial Lecture by Professor T. N. A. Jeffcoate: Premalignant Lesions of the Vulva.

ROYAL FREE HOSPITAL, Gray's Inn Road, London W.C.—(1) 4 p.m., Dr. John Higginson (Kansas City): Cirrhosis—Comments on Aetiology. (2) 5.15 p.m., Dr. Felix Wroblewski (New York): IBM (Computer) Diagnosis.

SOCIETY OF MEDICAL OFFICERS OF HEALTH: SOUTHERN BRANCH.—At the Castle, Winchester, 3 p.m., Dr. Mary Sheridan: Services for the Young Child with Impaired Hearing.

Thursday, April 13

ALFRED ADLER MEDICAL SOCIETY.—At Medical Society of London, 8 p.m., Dr. H. P. Tarnesby: Use of Hypnosis in Psychotherapy.

LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION.—At Royal Free Hospital Medical School, 8.30 p.m., Dr. Mary Sheridan: Learning Difficulties of Young Handicapped Children; Dr. Margaret Reinhold: Word Blindness.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Lumleian Lecture by Professor L. J. Witts: Some Aspects of the Pathology of Anaemia—(2) The Megaloblastic Anaemias.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor T. J. Butler: Effect of Gastrectomy on Pancreatic Function in Man.

WEST LONDON MEDICO-CHIRURGICAL SOCIETY.—At Royal Society of Arts, Adelphi, W.C., 8.30 p.m., Cavendish Lecture by Colonel Robert Henriques: Expression of Experience.

Friday, April 14

MIDLAND CENTRE FOR NEUROSURGERY, Holly Lane, Smethwick, Birmingham.—8 p.m., Mr G. F. Rowbotham: Circulations of the Brain, with Their Surgical Implications.

PLYMOUTH MEDICAL SOCIETY.—At North Friary House, 8.30 p.m., Professor J. H. Burn, F.R.S.: Hypotensive Drugs.

Saturday, April 15

CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—At Lecture Room "B," Addenbrooke's Hospital, symposium on neurology. *Morning:* 10.15 a.m., Dr. P. F. Roe: Headaches; 11.30 a.m., Dr. R. R. P. Hayter: Demonstration of Electrical Diagnostic Methods in Neurology; 12.15 p.m., Dr. M. F. T. Yealland: Facial Pain. *Afternoon:* 2.30 p.m., Examination of the Nervous System and Clinical Demonstration.

MIDLAND THORACIC SOCIETY.—At Worcester Royal Infirmary, 3 p.m. Symposium: Carcinoma of Bronchus.

Sunday, April 16

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—10.15 a.m., Mr. W. D. Doey: Seminar—Common Throat, Nose, and Ear Conditions.

APPOINTMENTS

SOUTH-WESTERN REGIONAL HOSPITAL BOARD.—G. Sheers, M.D., Temporary Consultant Chest Physician Plymouth Clinical Area; C. V. Mehendale, M.B., M.S., Registrar in Plastic Surgery, Frenchay Hospital, Bristol; P. M. J. Bennett, M.B., B.Chir., Medical Registrar, Cossham-Frenchay Group of Hospitals; B. H. Burns, M.B., Ch.B., D.Obst.R.C.O.G., and B. James, M.B., B.Ch., Psychiatric Registrars, Glenside and Barrow Group of Hospitals; G. Berry, M.B., Ch.B., D.Obst.R.C.O.G., D.A., and I. G. Cobham, B.M., B.Ch., Anaesthetic Registrars to Bath Group of Hospitals; R. T. Southwood, M.B., F.R.C.S., Registrar in Orthopaedic and Traumatic Surgery, Torquay and Exeter; D. A. Gandhi, M.B., B.S., D.T.M.&H., Medical Registrar, Royal Cornwall Infirmary, Truro; P. C. Sen Gupta, M.B., B.S., D.G.O., M.R.C.O.G., Registrar in Obstetrics and Gynaecology, Gloucestershire Royal and City Maternity Hospitals, Gloucester (reappointed).

BIRTHS, MARRIAGES, AND DEATHS

DEATHS

Abraham.—On March 21, 1961, Thornhill, Aughton, Ormskirk, Lancs, Everard Cecil Abraham, *M.C.*, M.D.

Chevallier.—On March 24, 1961, at Ravenstone, Olney, Bucks, Claude Lionel Chevallier, M.R.C.S. L.R.C.P., D.T.M., aged 91.

Cummings.—On March 15, 1961, at Law Hospital, Carluke, Ian Bruce Cummings, L.R.C.P.&S., L.R.F.P.S., of 35 Hope Street, Lanark.

D'Ewart.—On March 28, 1961, at his home, 4 Endon Drive, Manchester, John Thomas D'Ewart, M.B., aged 88.

De Lacey.—On February 23, 1961, William De Lacey, M.R.C.S., L.R.C.P., aged 56.

Deshmukh.—On December 21, 1960, at the Derbyshire Royal Infirmary, Gangadhar Narayan Deshmukh, M.B., B.S., D.A., of 24 Allestree Lane, Allestree, Derbys, aged 50.

Dunstan.—On March 20, 1961, at Torbay Hospital, Torquay, Devon, Robert Dunstan, M.R.C.S., L.R.C.P., aged 83.

Fearnley.—On March 15, 1961, at Birchgrove, The Breach, Devizes, Allan Baines Fearnley, M.D.

Fowler.—On March 16, 1961, at 5 Buckingham Mount, Victoria Road, Leeds 6, Edwin Samuel George Fowler, M.R.C.S., L.R.C.P., aged 86.

Gibbs.—On March 8, 1961, at 64 Parkstone Avenue, Emerson Park, Hornchurch, Essex, Augustus Edward Gibbs, L.M.S.S.A., L.R.F.P.S.

Harper.—On March 24, 1961, Robert Alexander John Harper, M.D., of 13 Lynedoch Place, Edinburgh, formerly of Dulwich, London S.E., aged 81.

Humphreys.—On February 12, 1961, Evelyn Bertha Berenice Humphreys, M.B., Ch.B., of Blenheim Cottage, Wargrave, Berkshire.

Pfeil.—On March 15, 1961, Enid Maud Pfeil, M.B., B.S.

Seymour.—On March 17, 1961, at 2 South Drive, Ruislip, Middlesex, Edith Ellen Seymour, L.R.C.P.&S., L.R.F.P.S., aged 96.

Swatman.—On March 17, 1961, at Bournemouth, Helen Swatman, M.B., aged 92.

Williams.—On March 16, 1961, at Aberffrwd House, Caergarw, Mountain Ash, Glam., Roger Llewellyn Williams, D.S.O., *M.C.*, L.R.C.P.&S., L.R.F.P.S., D.P.H., aged 83.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Firm Mattresses

Q.—*The firm bed advocated by our orthopaedic colleagues for ordinary use is presumably best achieved with a combination of a strong spring mattress covered by a hair mattress. The cost of a hair mattress is now so great that I wonder if there is any modern and cheaper substitute with a similar consistence. Is there a polyurethane foam or other synthetic that has the necessary combination of easy surface-give, underlying firmness, and persistent power of recovery?*

A.—The only substitute for a hair mattress that I know of is the "dunlopillo" mattress, which, in fair depth, gives comfort and the necessary lack of sagging which is what the orthopaedic surgeon desires. Some of the interior spring mattresses, when firm, are also perfectly satisfactory, since all that is needed is a flat surface that does not sag too much under the body weight or from prolonged use. Plastic foam would be hard enough, but I do not know if it is manufactured in the form of a made-up mattress.

Recording Heart and Lung Sounds

Q.—*How can heart and lung sounds be recorded on tape?*

A.—Heart sounds and murmurs may be satisfactorily recorded on tape, but it is necessary to have a pre-amplifier with suitable filters between the microphone and the tape-recorder. The microphones usually used are those of the piezo-electric type and are most conveniently made up into a small suction cup which adheres to the chest wall. These are connected to a small pre-amplifier which has a three or more position filter-switch, so that low, medium, and high frequency sounds may be recorded. The output from this may be fed into any good quality tape-recorder, preferably recording at a speed of 7½ in. (19 cm.) per minute. A suitable microphone and amplifier could probably be purchased from either the Cambridge Instrument Company, Cambridge, or from Messrs. Cardiac Recorders, of 8a Marylebone Mews, London W.1.

Immunizing an Allergic Child

Q.—*Is it wise to undertake any immunizations in a child aged 1 with a history of eczema following vaccination, and a family history of urticaria in one sibling and death from angioneurotic oedema in another? This child showed a small red flare on prick-testing with 1/10 solution of formol toxoid, and a minimal triple reaction on prick-testing with 1/10 solution of penicillin.*

A.—Such a child is certainly a problem to the immunologist. Whooping-cough vaccine should not be contemplated: the risk of an encephalitic reaction (as well as of severe local and general reactions) must be considered. At the age of 1 the child is past the worst period of severe whooping-cough, and it would be preferable to leave him unprotected in the hope that if he did get an attack it would be a relatively mild one. An attempt, however, should be made to immunize against diphtheria and tetanus. Only by successful active immunization against these can the child be protected against the obvious dangers which would arise, in the event of exposure to either disease, from giving antitoxin. The attempt should be made with a trial dose of diphtheria and tetanus vaccine—0.1 ml. of a 1 in 10 dilution—given deep subcutaneously or intramuscularly: syringe, needle, and adrenaline solution (1 in 1,000) should, of course, be in readiness. If there were no *general* reaction within half an hour, 0.1 ml. of undiluted vaccine should be given. If after another half-hour there were no *general* reaction, the full dose (0.5 ml.) of vaccine should be given. Skin tests are not advised, since local reactions to them do not necessarily indicate an undesirable, or dangerous, degree of sensitivity to a particular serum or vaccine.

Whether or not immunization against diphtheria and tetanus is accomplished, an attempt should be made, taking the same precautions, to immunize against poliomyelitis. In this case the risk of a reaction is much less. Reinforcement of diphtheria and tetanus immunization should similarly be attempted at school-entry and again at the age of 8 to 9 years. To summarize, such a child poses a problem; but not an insoluble one: attempts at immunization should be made, but always with thoughtful precautions.

Anticoagulants in the Tropics

Q.—*Should patients on anticoagulants reduce their dose when travelling in the tropics? I understand that excessive sweating increases the prothrombin time.*

A.—Many factors influence the effectiveness of anticoagulants of the coumarin series, notably the susceptibility of the individual, rate of absorption from the gastrointestinal tract, the body stores of vitamin K, the rate of metabolism of the anticoagulant, and its rate of excretion. It follows, therefore, that any degree of malnutrition will tend to increase the effect of the anticoagulant, as will impairment of liver function, infection, or renal disease. Coumarin-type anticoagulants might well be expected to act more powerfully on the visitor to the tropics, when excessive sweating may be associated with oliguria, impaired renal function, and salt deficiency. Gastroenteritis may aggravate fluid loss, fever may be contracted, or liver function temporarily compromised by unusual food or alcoholic excess.

While it may not always be necessary to reduce the dose of anticoagulant, scrupulous control of prothrombin time would seem a wise precaution while travelling in the tropics.

Chloramphenicol Toxicity

Q.—*The ship in which I am a surgeon has a good supply of chloramphenicol capsules 250 mg. I have used it at sea for conditions such as gastro-enteritis, tonsillitis, gonococcal infections, and subacute and acute appendicitis. What is the risk of agranulocytosis from chloramphenicol and is this influenced by the dose? Is there any drug which may be given simultaneously to lessen the risk?*

A.—Ordinarily chloramphenicol is safe to use when definitely indicated and when used in the proper way. It should only be given when the infecting organism responsible for the pathological condition is sensitive to chloramphenicol. Then it should be given in full doses for a maximum period of about 5 to 7 days. It is bad practice, and a dangerous one, to continue treatment for longer or indefinite periods, and still worse to repeat courses of treatment with only short intervals of a few weeks between them. Equally, a course of long-continued small doses, followed by a period of larger doses, is dangerous. In these ways the cells in the marrow may become sensitized to further doses, or inhibited partially or completely—leading to the production of severe and usually fatal agranulocytosis, aplastic anaemia, secondary thrombocytopenic purpura, or acute leukaemia. I have seen all of these happen. I also saw relatively large numbers of cases on a recent Eastern tour. The size of dose is not always the main initiating factor—small or large doses may be adequate to trigger off the marrow damage in suitably sensitive or sensitized patients.

Avoidance of the improper or indiscriminate use of chloramphenicol is the real prophylactic measure, for there is no known drug that can be given to lessen the risk.

(See also leading article at p. 1019.)

Amelogenesis Imperfecta

Q.—*My daughter's first teeth were hyperplastic. She is now 10 years old and her second dentition is of the same nature. The enamel is there but is very rough and therefore stains. Is there any dentifrice or solution which will remove this staining?*

A.—It is impossible to give a complete answer to this question without a clinical examination. It would appear probable, however, that a congenital disorder, amelogenesis imperfecta, is the cause of the condition. Should this be the case, no form of dentifrice or teeth-brushing is likely to produce any improvement. It is possible, however, ultimately to restore these teeth by means of jacket crowns, and thereby produce an aesthetically satisfactory result. The construction of such a large number of crowns is best carried out by a specialist in this field. It should be noted that children with this abnormality frequently stop brushing their teeth because it appears to be a waste of time. They tend, therefore, to get gingival trouble, and it is doubly important that correct oral hygiene should be maintained by brushing—particularly the gums from the gums to the teeth. This should be done vigorously with a soft brush.

Blood-tests in Second Pregnancy

Q.—*Why is it necessary to test for antibodies when a woman is first seen in her second pregnancy although tests in her previous pregnancy showed no antibodies and the first baby was not affected (presuming that the mother had not been transfused or had an abortion or miscarriage between the pregnancies)?*

A.—Rh antibodies may develop for the first time in a first labour, and late in that labour, and the baby be unaffected. It is therefore wise to test every Rh-negative woman at the first visit in every pregnancy; if antibodies are then present she can at once be referred for booking for hospital delivery, and the titre of antibody can be used as a baseline for comparison with later test results. It is common practice now to repeat the whole National Blood Transfusion Service blood test—ABO and Rh grouping and Kahn reaction—at the first visit in every pregnancy in every woman, for laboratory error, although uncommon, is not unknown.

Premedication and Induction of Anaesthesia

Q.—*From lack of other facilities I have to use open ether for anaesthesia. I find induction with vinyl ether and then ether sometimes stormy. What would be the best premedication to give? Is pethidine with added levallorphan suitable, or would it mask the depth of anaesthesia?*

A.—The question suggests that a stormy induction of anaesthesia is related to the premedication. This is not necessarily so. It is just as likely due to lack of expertise on the part of the anaesthetist. Criteria for the "best premedication" certainly include assistance in making induction easier. Mostly, however, they lie in the direction of the quality of the sedation and in the absence of such undesirable side-effects as vomiting and respiratory depression. All sedatives tend to make "open" methods of administration a little more difficult because respiration is in varying degree depressed. In addition, these drugs tend to mask, or modify, the so-called signs of anaesthesia. If no sedative is given, respiration is active and induction of anaesthesia is generally rapid, even in the hands of a moderately skilled anaesthetist. The bigger the dose of sedative the quieter is the patient beforehand, but the more respiration is depressed the more difficult does induction become with open methods. If the anaesthetist wishes to administer pethidine before anaesthesia, then the addition of levallorphan will minimize any respiratory depression due to the pethidine.

NOTES AND COMMENTS

Treatment of Kerosene Poisoning.—Dr. A. WARD GARDNER (Esso Refinery, Fawley, Southampton) writes: In his reply ("Any Questions?" February 18, p. 521) your expert omits to answer the question, "Is there any basis for the statement that the stomach ought not to be washed out in cases of kerosene (paraffin) poisoning?" There is very firm evidence in support of this view, and I would suggest that your questioner be referred to recent correspondence on the subject.[1–4] My own view is that absorption of kerosene is not a serious problem, while aspiration pneumonia is preventable but untreatable, and is the cause of death in kerosene poisoning.

REFERENCES
1 Capel, E. H., and Ward Gardner, A., *Lancet*, 1960, 1, 282.
2 George, B., ibid., 1960, 1, 826.
3 Capel, E. H., and Ward Gardner, A., ibid., 1960, 1, 1412.
4 George, B., ibid., 1960, 2, 318.

OUR EXPERT replies: I deliberately did not answer this question, having already read the correspondence between Dr. Capel and Dr. Ward Gardner on the one hand, and Dr. George on the other, because, in my view, there is great danger in being too dogmatic, and hence this decision must rest with the clinician. Clearly, each case must be treated on its merits and according to the technical ability of the person in charge. It must be remembered, for example, that fluid smelling of kerosene may contain other much more toxic substances.

Epidermolysis Bullosa.—Dr. E. J. MOYNAHAN (Guy's Hospital, London S.E.1) writes: My attention has been drawn to an answer given to a question on the treatment of epidermolysis bullosa ("Any Questions?" February 18, p. 522) in which it is stated that there is no effective treatment for the condition. This has not been my experience, and I have now treated a number of children suffering from the severe dystrophic form of the disease effectively with corticosteroid preparations at the Hospital for Sick Children, Great Ormond Street. I have shown to the clinical and dermatological sections of the Royal Society of Medicine one extremely severe case with pharyngeal stenosis sent to us with a view to gastrostomy in which cortisone produced sufficient relief to obviate the need for this, and rendered the boy fit for plastic reconstruction of his cripplingly deformed hands. It is true that some cases do not benefit from steroid therapy, or, to be more precise, the dosage required to control the blistering may be much too high to continue with, but it would be most unfortunate if any of your readers formed the opinion that these agents are ineffective in the treatment of these conditions, because delay in beginning treatment may lead to much higher doses being ultimately needed to control the blistering. This is especially true of those infants who have blisters at various sites at birth or have mucosal lesions in the first week of life. The simple variety of the disorder, which is transmitted as a genetic dominant, is usually not severe enough to justify long-term suppressive steroid therapy. It certainly never imperils life, and mutilating deformities are not produced by the much more superficial blisters met with in the simplex form of the disease. The cases I refer to will be published in a forthcoming number of the *Proceedings of the Royal Society of Medicine*.

OUR EXPERT replies: I have seen this case of Dr. Moynahan's and entirely agree with his remarks, which I think he puts quite fairly. I do not think that Dr. Moynahan would suggest that steroids would cure the condition but that their continued administration would control it in some cases.

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